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2. Patent application number *(The Patent Office will fill in this part)*	**9824604.4**
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Hewlett Healthcare Limited No 1 Mill The Wharf, Shardlow Derby DE72 2GH United Kingdom
Patents ADP number *(if you know it)*	07208812001
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4. Title of the invention	TREATMENT OF ALLERGIC CONDITIONS
5. Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	ERIC POTTER CLARKSON PARK VIEW HOUSE 58 THE ROPEWALK NOTTINGHAM NG1 5DD
Patents ADP number *(if you know it)*	1305010
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Request for preliminary examination and search *(Patents Form 9/77)*	NO
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11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson
ERIC POTTER CLARKSON

Date
10 November 1998

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TREATMENT OF ALLERGIC CONDITIONS

The present invention relates to the treatment of allergic conditions, in particular allergic conditions which relate to the nature of the food or drink consumed by the patient. Allergy to ingested substances can manifest itself in a wide range of symptoms affecting any organ in the body. Commonly it affects particularly the gastrointestinal tract, the skin, the lung, the nose and the central nervous system. Allergic reactions to ingested substances affecting these organs can manifest themselves as abdominal pain, abdominal bloating, disturbance of bowel function, vomiting, rashes, skin irritation, wheezing and shortness of breath, nasal running and nasal blockage, headache and behavioural changes. In addition in severe food allergic reactions, the cardiovascular and respiratory systems can be compromised giving anaphylactic shock and in some cases death.

It is also recognised that in certain chronic diseases, allergy to ingested substances is the probable cause of the disease in a proportion of patients. These diseases include anaphylactic shock, atopic dermatitis, chronic urticaria, asthma, allergic rhinitis, irritable bowel syndrome, migraine and hyperactivity in children. It is also possible that food allergy may be a factor in certain patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease).

This vast array of symptoms and diseases presents the medical practitioner with tremendous problems of diagnosis and management. In the absence of any reliable tests for food allergy other than double-blind, placebo-controlled, food challenges which are time-consuming,

expensive and potentially dangerous, many practitioners are often reluctant to regard allergy as the cause, and rely on symptomatic treatment for management. For example, wheezing and asthma are treated with bronchodilators, atopic dermatitis with topical corticosteroids, rhinitis with nasal decongestants and irritable bowel syndrome with anti-spasmodics.

One drug which has been investigated over the years for treating allergic conditions, particularly asthma, is sodium cromoglycate. This was initially launched in the 1960's by Fisons as an inhaled prophylactic treatment for asthma. In 1972, an insufflated powder formulation "Rynacrom" was introduced for nasal allergies, followed in 1975 by a more convenient nasal spray solution. In 1976, a dropper bottle solution called "Opticrom" was launched for eye allergies and, in 1978, an oral powder ("Nalcrom") was marketed initially for the treatment of inflammatory bowel disease and later for food allergy. However, various clinical studies have failed to confirm that the oral formulation of sodium cromoglycate is adequately effective in inflammatory bowel disease and this indication was withdrawn in the early 1980's.

The clinical efficacy of oral sodium cromoglycate (Nalcrom) has been reported as being variable with some authorities reporting good effects and others variable or poor effects.

The current "Nalcrom" formulation of sodium cromoglycate consists of a powder which is either taken by the patient as a solution (ie after dissolving the powder in water) or presented in a gelatin capsule which dissolves in the stomach. As one would expect, the various Fisons

patent specifications concerning sodium cromoglycate list a vast number of theoretical formulations of the drug, practically none of which have been put into effect. Thus, GB 1 423 985 discloses an enteric coated composition intended to make the drug available "at an appropriate part of the gastro-intestinal tract" (unspecified) and GB 1 549 229 discloses a gelatin capsule containing granules of the drug, for oral use in the treatment of allergic conditions. Both of these two patent documents date from the 1970's and there is no indication that the performance of these compositions in practice was investigated.

The previously proposed gelatin capsules of sodium cromoglycate are, we consider, of low bioavailability because the sodium salt of the drug is converted in the acidic conditions of the stomach into insoluble and inactive cromoglycic acid. Although, in the alkaline medium of the duodenum, the cromoglycic acid may convert back to a salt, this is unlikely to be the sodium salt and is more likely to be an insoluble and inactive salt such as a calcium salt. The enteric-coated formulations which have been proposed previously, at least on paper, similarly may be of low bioavailability because the sodium cromoglycate is released from the enteric coating into the duodenum in a lump that does not dissolve, rather than being dispersed evenly throughout the food material passing through the small intestine. A gel may form round the lump of sodium cromoglycate on exposure to aqueous liquid that inhibits dispersion of the sodium cromoglycate. The gel may seal the surface of the sodium cromoglycate, preventing further wetting of sodium cromoglycate remaining inside the gel.

We have now investigated the matter more closely and we have found that chromones such as sodium cromoglycate are effective in treating these various allergic conditions providing that they are formulated in a particular manner. In addition, the patient may first be selected according to a specific criterion.

A first aspect of the invention provides an oral drug delivery composition comprising a chromone wherein the chromone is made bioavailable in the small intestine following human oral administration, characterised in that the chromone is made bioavailable within 10, or preferably about 1, 2, 3, 4, 5, 6, 7, 8 or 9, minutes of exposure of the composition to simulated intestinal fluid.

We consider it to be desirable for the drug to be applied evenly and preferably temporally consistently across the surface of the mucosa in the small intestine prior to and at the same time as the surface of the mucosa is exposed to the food which is causing the allergy. However, we consider that the maximum concentration of sodium cromoglycate to which the mucosa is exposed may be more important than the cumulative (ie time x concentration) exposure. Thus, low concentrations (for example, less than 0.05%w:v) of chromone may be biologically ineffective even if applied to the mucosa over a prolonged period. Intal nebuliser solution, for example, is used at a chromone concentration of 1% and Rynacrom, Lomusol and Opticrom are used at a chromone concentration of 2% or (in some cases) 4%. We consider it may be beneficial to achieve a concentration of at least 0.05%, preferably 0.1%, 0.2%, 0.5%, 1%, 2% or 4% (w:v) at the mucosal surface, preferably at

least 2 to 4 times a day, or at the same time or before exposure to allergen, of a chromone such as sodium cromoglycate.

Calculations of concentrations of scg that may be achieved in the gut by present formulations of scg are discussed in Examples 5 and 6. Previous formulations may achieve a maximal concentration of less than 0.04% w:v.

We consider that it is beneficial that the chromone is made bioavailable as rapidly as possible on entering the small intestine following human oral administration (ie preferably within the first 10 minutes of the composition being exposed to intestinal fluid). This may have the benefits of making the chromone bioavailable in a smaller volume of the intestinal contents than if release is slower (ie occurs over longer than a 10 minute period), thus achieving a higher local concentration of the chromone. Successive portions of the small intestine may be exposed to the chromone as the intestinal contents into which it was released progresses along the small intestine. Further, we consider that it may be particularly beneficial that substantially all of the chromone is made bioavailable within the duodenum (the first approximately 25 cm of the small intestine) such that the entire jejunum (ie the portion of the small intestine following the duodenum, of approximately 3 m in length) is exposed to the maximum concentration of chromone. The jejunum may be the most important portion of the small intestine in relation to allergic conditions relating to ingested substances, as discussed below, and therefore we consider that it may be the most important portion to expose to a chromone.

Chromones such as sodium cromoglycate are poorly absorbed in the gut. Less than 1% of ingested sodium cromoglycate may be absorbed during passage through the gut (see, for example, Moss *et al* (1971) *Toxicol & Appl Pharmacol* **20**, 147-156; Walker *et al* (1972) *J Pharm Pharmac* **24**, 525-531). Chromones are also not significantly metabolised in the gut (see for example Moss *et al* (1971) and Walker *et al* (1972), above). Thus, the concentration of chromone in the small intestine is unlikely to be altered significantly by uptake or metabolism of the chromone following release of the chromone. Mixing of the intestinal contents may reduce local concentration. Net absorption of fluid from the small intestine may increase the concentration of chromone, as described in Examples 5 and 6. Thus, the concentration in the upper jejunum may be approximately double that in the mid-duodenum. Pancreatic and biliary secretion into the small intestine may reduce the concentration of chromone in later sections of the intestine.

As only a small proportion of chromone is removed from the small intestine by absorption or metabolism, early release of the chromone in the small intestine, as described herein, may be preferable to release of the chromone in more than one section of the small intestine, as it may maximise the concentration of chromone to which the mucosa of the small intestine is exposed.

The chromone is preferably (sodium) cromoglycate or nedocromil (sodium). References to sodium cromoglycate hereafter refer to the class of chromones as well as to the individual compound.

The composition may be formulated, for example, as a tablet or capsule or as a unit dose that may be suspended in a liquid immediately prior to use. The tablet or capsule may have an enteric coating. The enteric coating (and the capsule, if appropriate) may dissolve or disintegrate, preferably rapidly (ie in less than 10 minutes), when it reaches alkaline conditions, for example on entering the small intestine.

Alternatively, the tablet or capsule may not have an enteric coating but may disintegrate in the stomach to release an enteric coated composition comprising sodium cromoglycate. Similarly, the suspendible unit dose formulation may comprise an enteric coated composition comprising sodium cromoglycate.

It may be preferred that if the formulation is a capsule it is not an enteric coated capsule. This is because the requirement for disintegration of both an enteric coat and a capsule may result in slower exposure of the composition comprising sodium cromoglycate to the intestinal fluid than may be achieved with a enteric coated tablet formulation.

A drug can be made "bioavailable", for example, either as a result of the coating disintegrating or as a result of the coating becoming porous, followed by dispersal and dissolution of the drug. Preferably, the coating disintegrates. For a chromone, as discussed above, dispersal and dissolution of the drug may require that the chromone is rapidly dispersed on exposure to an aqueous environment, for example intestinal fluid, or that the chromone is exposed to the aqueous environment in small aliquots that are not big enough for a non-dispersible gel to form.

Thus, when the chromone is formulated with a larger mass of disintegrant, for example microcrystalline cellulose in a ratio of 2.5:1 to the chromone, the disintegrant may promote rapid disintegration of the tablet before a gel has formed. When the chromone is formulated as enteric coated pellets of less than 5 mm diameter, preferably less than 1.5 mm diameter, the surface area:mass ratio of the chromone exposed to the aqueous environment in each pellet may be sufficiently high that the chromone disperses and dissolves rather than forming a gel. Thus, release of a chromone from an enteric coated dry formulation requires disintegration or porosity of the coating and dispersal and dissolution of the chromone.

It is preferred that the composition is such as to prevent release of the sodium cromoglycate from said pellet in gastric fluids, but to permit release (including dispersion and dissolution) of the sodium cromoglycate from said pellet in intestinal fluids, preferably within 10 minutes of exposure to the intestinal fluids.

The rate may be measured *in vitro* as a dissolution rate of said unit in simulated gastric and intestinal fluids, when measured in a flow through cell (eg Sotax Dissotest CE6, equipped with 12 mm cells) at 8 ml/min and 37°C. Typically, (a) not more than 10%, preferably not more than 5%, of the total sodium cromoglycate is released after two hours in simulated gastric fluid (eg USP, pH1.2, without enzymes) in said assembly, (b) from 15 to 90%, preferably from 20 to 95% or 100%, of the total sodium cromoglycate is released after two hours in simulated intestinal fluid (eg USP, pH 7.5, without enzymes) in said assembly.

The limiting factor in the making bioavailable of a chromone from an enteric release formulation may be the dispersion of the formulation and the dissolution of the chromone once the enteric coating has disintegrated or become porous (preferably disintegrated).

This may be measured by exposing the formulation without enteric coat (ie before the enteric coat is applied) to an aqueous buffer or to simulated intestinal fluid and observing the behaviour of the formulation and/or the degree of solubilisation of the chromone.

Thus, the tablet or pellet may be placed in 30ml of distilled water at 20°C and prodded at various time intervals. On prodding, the tablet or pellet may remain intact or may disintegrate. It is preferred that the tablet or pellet disintegrates on prodding after (in order of preference) 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 minute or 30 second exposure to the liquid. It is particularly preferred that the tablet or pellet disintegrates on prodding after less than 2 minutes' exposure to the distilled water.

It may be found that if a formulation, particularly a tablet, comprising a chromone does not disintegrate after 1 or 2 minutes exposure, that it is very unlikely to disintegrate after further exposure, even for several hours. This may be because if a chromone gel is able to form in the first few minutes, this may hold the tablet together.

The concentration of a solution of a chromone, for example sodium cromoglycate, may be measured by measuring the absorbance of the solution at 326 or 325nm, or by chromatography, for example high performance liquid chromatography (HPLC), techniques, as is well

known to those skilled in the art. Thus, these techniques may be used to measure the rate at which the chromone enters solution from a formulation of the invention. It will be appreciated that when sampling, the liquid containing the tablet(s) or pellet(s) under test should be mixed in a standardised way, which should be sufficient to ensure homogeneity of the liquid, but not so vigorous as to lead to disintegration of the tablet or pellet. Suitably, the sample liquid may be gently swirled for 10 seconds at minute intervals, prior to removal of an aliquot for assay.

It is preferred that at least 50%, 60, 70, 80 or 90% of the chromone has entered solution after 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 minute exposure to distilled water at 20°C in a volume of 30 ml.

In an embodiment of the first aspect of the invention, the oral drug delivery composition further comprises disintegrant at a ratio of at least 1.5:1 (w:w) of disintegrant to chromone.

A second aspect of the invention is a an oral drug delivery composition comprising a chromone wherein the composition further comprises disintegrant at a ratio of at least 1.5:1(w:w) of disintegrant to chromone. Preferably, the chromone is made bioavailable in the small intestine following human oral administration.

The following preferences apply to both the above aspects of the invention.

It is preferred that the ratio of disintegrant to chromone is at least 2:1, 2.5:1, 3:1, 4:1 or 5:1. Ratios are expressed as weight:weight ratios.

In a particularly preferred embodiment, the ratio of disintegrant to chromone may be 2.5:1.

In the disintegration/solubilisation assay described above, the gentle swirling may be sufficient to produce after 1 or 2 minutes' exposure to water a "snow-storm" type appearance with a tablet comprising 261 mg of the disintegrant microcrystalline cellulose and 100mg sodium cromoglycate granules, as described in Example 1.

The term "disintegrant" is well known to those skilled in the art, as discussed in Remington's: "The Science and Practice of Pharmacy", 19th Edition. A disintegrant may be a substance or mixture of substances that may be added to a pharmaceutical tablet in order to facilitate its breakup or disintegration after administration, or in an *in vitro* test designed to assess the disintegration of a tablet (as described above or as also described in Remington's: "The Science and Practice of Pharmacy", 19th Edition). Disintegrants may be grouped as starches, clays, celluloses, algins, gums and cross-linked polymers.

Examples of disintegrants that may be used in the present invention include corn and potato starch, Veegum HV, methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose. Croscarmelose (a cross-linked cellulose), crospovidone (a cross-linked polymer), sodium starch glycolate (a cross-linked starch) and cross-linked PVP have been termed superdisintegrants as they are typically

effective at 2 to 4% of a tablet composition. Acdisol is a further example of a superdisintegrant.

It will be appreciated that one or more than one disintegrant may be used in a composition of the invention. Thus, the ratio cited above of disintegrant to chromone may be the ratio of a particular disintegrant to chromone or the ratio of total disintegrant to chromone.

A preferred disintegrant is microcrystalline cellulose. Particularly preferred forms of microcrystalline cellulose include Avicel, in particular Avicel PH101 or PH102 (FMC Corporation, Pharmaceutical Division, 1735 Market Street, Philadelphia, PA 19103). Avicel PH301 and PH302 (from the same supplier) are slightly denser than Avicel PH101 and PH102 and may also be preferred, for example in capsule formulations.

It is preferred that a superdisintegrant as listed above is not used as the sole disintegrant in the ratios given above, as a superdisintegrant may itself form a gel which may retard dispersal of the composition. However, a superdisintegrant may be used in a composition of the invention in combination with a disintegrant, for example microcrystalline cellulose. Thus it is preferred that a superdisintegrant does not comprise more than 20, 30, 40, 50, 60, 70 or 80% of the mass of the formulation.

It will be appreciated that in the prior art, disintegrants are routinely used as up to about 20% of the weight of a tablet. It will further be appreciated that, as set out in, for example, GB 1 549 229, the

preference in the art has been to formulate sodium cromoglycate in the substantial absence of excipients, such as disintegrants.

Whilst not intending to be bound by theory, it is considered that the disintegrant may aid bioavailability of the chromone by aiding its dispersion and/or dissolution on exposure to the intestinal contents. The disintegrant may swell on exposure to aqueous liquid and help disperse the chromone. It is considered that in the absence of disintegrant in a ratio of at least 1.5:1, 2.0:1 or 2.5:1 (w:v) disintegrant:chromone, the chromone may form a gel on exposure to aqueous liquid that inhibits dispersion of the chromone. The gel may seal the surface of the chromone, preventing further wetting of chromone remaining inside the gel. The enteric coated tablet may enter the duodenum, the enteric coat dissolve and the tablet disintegrate rapidly to release and disperse the chromone, which may then dissolve.

The chromone may be granulated before being mixed with the disintegrant, for example microcrystalline cellulose. A lubricant, for example magnesium stearate, as is well known to those skilled in the art, may be added. Further examples of lubricants may be given in Remington *supra* and in Martindale: The Extra Pharmacopoeia, 32nd edition. A tablet may then be formed from the granules and disintegrant, using methods well known to those skilled in the art, and as described in Example 2. The ratio of disintegrant to chromone granules in the tablet may be 2.5:1. As is known to those skilled in the art and as described in Remington *supra*, the pressure employed in tabletting may affect the dispersal of the tablet and may require adjustment depending on the excipients used.

The granules may be of 25 to 250 μm, 25 to 500 μm, 200 to 1100μm, or 100 to 750 μm diameter. These figures preferably refer to at least 50%, preferably at least 75%, 90%, 95%, 99% and most preferably 100% of the granules in the formulation. A median particle diameter of about 200μm may be preferred.

The chromone may be granulated by known techniques, for example using a wet granulation method, as described in Examples 1 or 2. It will be appreciated that a diluent may be added to the chromone to aid fluidisation during granulation. The diluent may be a disintegrant. For example, microcrystalline cellulose may be used as a diluent during granulation, for example at about 10% of the weight of the chromone.

A surfactant may be added to the chromone, for example during granulation, as described in Example 2. It is preferred that the surfactant is an amphoteric surfactant. Use of a surfactant may mean that a formulation comprising the surfactant has similar properties to that of a formulation with a higher ratio of disintegrant to sodium cromoglycate but no surfactant. The term "amphoteric surfactant" is well known to those skilled in the art. Such surfactants (which may also be known as ampholytic surfactants) possess at least one anionic group and at least one cationic group, and can therefore have anionic, non-ionic or cationic properties depending on the pH. If the isoelectric point of the molecule occurs at pH7, the molecule is said to be balanced. Amphoteric surfactants may have detergent and disinfectant properties. Balanced amphoteric surfactants may be particularly non-irritant to the eyes and skin.

It will be appreciated that the composition should not contain ingredients that may cause irritation to the skin or mucosa, even on prolonged use. Compounds to which sensitisation may occur should be avoided. Thus, balanced amphoteric surfactants may be preferred.

Examples of amphoteric surfactants include aminocarboxylic acids, aminopropionic acid derivatives, imidazoline derivatives, for example a carboxylated imidazoline derivative, dodicin, pendecamaine or long-chain betaines, Nikkol AM101® (2-alkyl-*N*-carboxymethyl-*N*-hydroxyethyl imidazolinium betaine), Nikkol AM310® (lauryldimethylaminoacetic acid betaine), Nissan Anon #300 (12 w/v% alkyldiaminoethylglycine hydrochloride, 3 w/v% alkyldiethylene-triaminoglycole hydrochloride; Inui Shouji Co, ADG), C31G (a mixture of alkyl betaines and alkyl amine oxides), N-tetradecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate) or cocamidopropyl betaine. Any of these may be used but it is preferred that a compound is used that has not been suggested to be linked with allergy, particularly by the oral route. Instances of allergy to cocamidopropyl betaine, when used in shampoo, have been reported (De Groot *et al* (1995) *Contact Dermatitis* 33(6), 419-422).

It will be appreciated that an amphoteric surfactant may be supplied (as an "amphoteric surfactant" or amphoteric surfactant preparation) packaged or compounded with other substances by the manufacturer, and that references to an amphoteric surfactant encompass an amphoteric surfactant alone and a preparation supplied as an amphoteric surfactant by the manufacturer.

A preferred amphoteric surfactant may be cocamidopropyl betaine, which may be supplied, for example as a 30% aqueous solution, for example as Incronam 30 (Croda Oleochemicals, Cowick Hall, Snaith, Goole, East Yorkshire, DN14 9AA, UK).

The amphoteric surfactant may be disodium coacoamphodiacetate. It is preferred that the disodium coacoamphodiacetate is packaged or compounded with lauryl sulphate and hexylene glycol, as is known to those skilled in the art. A preferred preparation of disodium coacoamphodiacetate has the following composition:

disodium coacoamphodiacetate	14%w/w
sodium lauryl sulphate	12.5%w/w
hexylene glycol	7%w/w
sodium chloride	3.9%w/w
lauryl alcohol	1.0%w/w
hydrochloric acid	1.0%w/w
sodium sulphate	0.25%w/w
formaldehyde	0.03%w/w
water	to 100%w/w

Such a preparation may be Miracare 2MCA/E™, supplied by Rhodia Limited, Poleacre Lane, Woodely, Stockport, Cheshire SK6 1PQ.

A further preferred surfactant is an amphoteric surfactant from a coconut base, for example sodium cocoamphoacetate. This may be supplied as Miranol (Rhodia Limited, as above), in particular Miranol Ultra C32.

A preferred preparation of sodium cocoamphoacetate has the following composition:

sodium cocoamphoacetate	30-32% w:w
sodium glycolate	1.8% w:w max
sodium chloride	7.6% w:w max
sodium monochloracetate	20 ppm max
colour (Gardner)	3 max
solids	38-41 w:w %
water	to 100 w:w %
pH (20% aqueous solution)	8.5-9.5

The surfactant may be added to about 0.001, 0.01, 0.1, 0.5, 1, 2, 5, 10, 20, 30, 40 or 50% (w:w) of the chromone. Preferably, it is added to about 2% (w:w) of the chromone. It is preferred that the above percentages refer to the active ingredient of an amphoteric surfactant formulation ie to the amphoteric surfactant component.

A further aspect of the invention is therefore an oral drug delivery composition comprising a chromone, wherein the composition further comprises an amphoteric surfactant, for example cocamidopropyl betaine or sodium cocoamphoacetate. Preferably, the chromone is made bioavailable in the small intestine following human oral administration, and still more preferably is made bioavailable within 10 minutes of exposure of the composition to simulated intestinal fluid.

A further aspect of the invention is the use of an amphoteric surfactant in the manufacture of a medicament for treating a patient with an allergic condition wherein the medicament is administered orally. It is preferred that the medicament comprises sodium cromoglycate.

In a less preferred granulation method, granules can be prepared by coating non-pareil seeds with the sodium cromoglycate or by forming a core comprising sodium cromoglycate dispersed therein. Suitable binding agents which may be used in forming such a core are known in the art. The excipients used to prepare the seeds may comprise one or more of pharmaceutically acceptable materials, eg sugar, starch, microcrystalline cellulose, waxes and polymeric binding agents, such as those listed below. The first layer on the non-pareil seeds may comprise the sodium cromoglycate and a water-soluble or water-insoluble polymer which acts both as binder for the sodium cromoglycate and as a rate-limiting layer for release of the sodium cromoglycate. Such polymers may be selected from cellulose derivatives, vinyl polymers and other high molecular polymer derivatives or synthetic polymers such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate, polyvinyl pyrrolidone, polyvidone acetate, polyvinyl acetate, acrylic polymers and copolymers, polymethacrylates and ethylene-vinyl acetate copolymer or a combination thereof. Preferred film-forming polymers are ethylcellulose or copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS) in aqueous dispersion form.

The optionally first rate-limiting layer on the seeds with homogeneously distributed sodium cromoglycate may comprise a water insoluble

polymer or a mixture of water insoluble polymers or a mixture of water soluble and water insoluble polymers mentioned above. It will be appreciated that it is preferred that any such rate-limiting layer does not prevent the sodium cromoglycate from being released from the formulation within 10 (or less; as set out above) minutes of the formulation being exposed to intestinal fluid or simulated intestinal fluid.

The coatings may optionally comprise other pharmaceutically acceptable materials which improve the properties of the film-forming polymers such as plasticizers, anti-adhesives, surfactants, and diffusion-accelerating or diffusion-retarding substances. Suitable plasticizers comprise phthalic acid esters, triacetin, dibutylsebacate, monoglycerides, citric acid esters and polyethyleneglycols. Preferred plasticizers are acetyltributyl citrate and triethyl citrate. Suitable antiadhesives comprise talc and metal stearates.

The amount of the first coating (if used) applied on the units may be in the range between 0.5% and 30% by weight, preferably between 1% and 15%. This amount includes in the relevant case the weight of the sodium cromoglycate as well. The amount of coating (which may be one or two coatings) applied on the units may be in the range between 1 and 50% or 5% and 60% by weight, preferably between 5% and 50% or 2% to 25%, calculated on the weight of the coated units. The remainder constitutes the weight of the seed or core. It is thus clear that the above percentages refer to the coating as a percentage of the final weight of the units after coating. Alternatively, the amount of the coating may be in the range between 5 and 120%, preferably between 5 and 100%, more

preferably between 5 and 50%, most preferably between 6 and 10% by weight of the weight of the seed or core or active ingredient.

For example, in one process, sodium cromoglycate powder (in which 90% of the particles may have a diameter of less than 30μm) is spray granulated in a fluid bed dryer in combination with water and HPMC to agglomerate the particles into larger particles.

Alternatively, the sodium cromoglycate can be mixed with a melt binder such as polyethylene glycol, heated to its melting point in a high shear mixer and cooled, as discussed in Example 3. This produces rather larger particles of about 200 μm, or 200 to 1100 μm.

The granules/particles may then be formed into a tablet (or alternatively packaged in a capsule) with a disintegrant in the ratios described, and the tablet (or capsule) enteric coated. Alternatively, the sodium cromoglycate may be granulated with the disintegrant in the ratios described and the granules formed into a tablet or packaged in a capsule which is then enteric coated.

It will be appreciated that a tablet in which the core has the above ratio of disintegrant to chromone may further be coated in disintegrant prior to any enteric coating. It is preferred that such a coating of disintegrant substantially does not comprise a chromone.

It will be appreciated that the composition may comprise more than one disintegrant. For example, different disintegrants may be mixed with

the chromone and be used as a further coat around the chromone-containing core.

It will be appreciated that it is preferred that the disintegrant does not comprise heavy metal or alkaline earth ions as a significant constituent (ie more than about 10, 20, 30 or 40 % w:w). Di-calcium phosphate, for example, comprises Ca^{2+} ions and may therefore not be suitable.

It will be appreciated that the composition may further comprise other compounds, for example bulking agents and/or lubricants and/or a surfactant. However, it preferred that the composition consists substantially of the chromone (which may comprise water), disintegrant, a lubricant, for example magnesium stearate and a surfactant, for example Miranol.

It is preferred that the composition does not comprise an allergen, particularly an allergen to which the prospective patient is thought to be allergic. However, a composition of the invention comprising such an allergen may be of use in desensitisation treatment, for example as described in WO85/00015.

It is also preferred that the composition does not comprise a physiologically acceptable pH regulating alkaline material in an amount sufficient to produce a significant pH change when released in the small intestine.

In a further embodiment of the first aspect of the invention, the composition comprises pellets of between 0.7 and 5 mm diameter, wherein each pellet is substantially spherical and has an enteric coating.

A further aspect of the invention is a oral drug delivery composition comprising a chromone, wherein the composition comprises substantially spherical pellets of up to 5 mm diameter, each pellet having an enteric coating. The composition may further comprise an amphoteric surfactant, as described above and further below. Preferably, the chromone is made bioavailable in the small intestine following human oral administration.

We have found that enteric coating of pellets that are not substantially spherical may not be effective. Although the pellets may appear to have been coated, we have found that the coating may disintegrate at a different pH from that intended. For example, a coating expected to disintegrate at a pH of about 5 or more may disintegrate at a pH of about 3.5.

By "substantially spherical" is meant that the pellet has the appearance of a sphere when examined by the unaided eye. It will be appreciated that it is preferred that both the uncoated and coated pellet are substantially spherical.

It is preferred that the pellets have a diameter of between 0.7 mm and 5mm, 4mm, 3 mm, 2 mm, 1.8 mm, 1.5 mm or 1.3 mm, preferably between 0.8 and 1.5 mm. It will be appreciated that these dimensions refer to the enteric coated pellet. It will further be appreciated that the

uncoated pellets may have dimensions between 0.5 mm and 4.8 mm, 3.8 mm, 1.8 mm, 1.6 mm, 1.3 mm or 1.1 mm, preferably between 0.6 mm and 1.3 mm. These figures preferably refer to at least 50%, preferably at least 75%, 90%, 95%, 99% and most preferably 100% of the pellets in the composition.

Substantially spherical pellets comprising a chromone may be prepared, for example, by mixing with a melt binder such as polyethylene glycol, heating to its melting point in a high shear mixer and cooling. The pellets are then dried in a fluid bed drier. The pellets may be referred to as melt pellets. An example of such a method of preparing the pellets is given in Example 2.

The melt binder may be an aqueous binder described above. Examples include polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC). PEG may be preferred as it may give a strong granule that is particularly suitable for coating.

As described above for the preparation of granules for formulation with a disintegrant, a surfactant, preferably an amphoteric surfactant may be added to the chromone, for example with the binder. Preferences for the amphoteric surfactant and the quantities that may be used are as described above.

The pellets or tablets or capsules may be enteric coated using a fluid bed based coating system or using the coating pan technique in a side vented pan, as well known to those skilled in the art.

It is preferred that the pellets are enteric coated such that the chromone is made bioavailable in the duodenum, as described above.

The polymers used to enteric coat a tablet, capsule or pellet may be selected from the group of anionic carboxylic polymers suitable for pharmaceutical purposes and being soluble only with difficulty at a low pH but being soluble at a higher pH, the pH limit for solubility being in the interval of pH 4 to pH 7.5, said group comprising cellulose acetate phthalate (for example Aquateric; FMC Corporation, Pharmaceutical Division, 1735 Market Street, Philadelphia, PA 19103), cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate and acrylic acid polymers eg partly esterified methacrylic acid polymers such as Eudragit L, Eudragit L100-55 and Eudragit S. These polymers may be used alone or in combination with each other or in combination with water insoluble polymers mentioned before. Preferred polymers are the Eudragits in aqueous dispersion form. The anionic carboxylic polymer may comprise 25 to 100% of the total polymer content.

The enteric coatings may optionally comprise other pharmaceutically acceptable materials which improve the properties of the film-forming polymers such as plasticizers, anti-adhesives, surfactants, and diffusion-accelerating or diffusion-retarding substances. Suitable plasticizers comprise phthalic acid esters, triacetin, dibutylsebacate, monoglycerides, citric acid esters and polyethyleneglycols. Preferred plasticizers are acetyltributyl citrate and triethyl citrate. Suitable antiadhesives comprise talc and metal stearates.

The amount of the enteric coating applied on the units is normally in the range between 1% and 50% by weight, preferably between 2% and 25%, still more preferably between 10-15%, most preferably about 12%, calculated on the weight of the coated units.

The capsule may be a gelatin capsule (for example, a capsule which consists essentially of gelatin) which may then enteric coated as described above. Suitable capsules are well known to those skilled in the art. The capsules should not be such that they may pass through the small intestine or even the whole gastrointestinal tract substantially intact. The capsules may be such that if they were used without the enteric coating they may release their contents in the stomach.

It is preferred that the enteric coating is chosen such that maximum disintegration of the coated capsules occurs within the small intestine (duodenum, jejunum, ileum), preferably within the duodenum. Preferably, substantially all of the administered chromone is made bioavailable from the duodenum onwards.

It is preferred that the tablet (or capsule) is able to pass through the stomach and into the small intestine (ie through the pylorus). Thus, it is preferred that the tablet may have a final weight of up to 500 mg for use in children, preferably between 300 and 500 mg. A larger tablet may be acceptable in adults. It is preferred that the tablet size is such that the tablet may be swallowed easily by a child (for example, has dimensions less than about 0.8 cm). It is preferred that each tablet contains less than an intended daily dose of sodium cromoglycate, so that more than one tablet may be taken per day, as discussed below.

If the tablet or capsule is not enteric coated and comprises pellets that are enteric coated then it is expected that the tablet or capsule will disintegrate in the stomach and release the enteric coated pellets into the stomach contents. Enteric coated pellets may therefore become mixed with the stomach contents and enter the duodenum with portions of the stomach contents. Once exposed to intestinal fluid in the duodenum, the enteric coat of each pellet may disintegrate, releasing pellets of sodium cromoglycate which may have a sufficiently large surface area:mass ratio that the sodium cromoglycate may enter solution.

For the above third aspect of the invention, it is preferred that the chromone is made bioavailable in the duodenum, as described above. However, it may be beneficial if differing groups or populations of the individual pellets have differing enteric coatings such that the drug content of the pellets is first made bioavailable at differing locations in the small intestine.

Two particular ways in which the drug can be made bioavailable at differing times, and therefore differing locations of the small intestine as the contents pass through the intestine, are to coat the pellets/tablets/capsules with differing thicknesses of the same enteric coating or to use differing enteric coating materials which dissolve at differing pH's. This may provide a non-pareil formulation. Both formulations take advantage of the fact that the pH of the contents of the intestine gradually rises as the contents pass from the stomach into and through the small intestine. Suitable enteric coatings are known in the art and are discussed in more detail below.

The enteric-coated pellets can be filled into capsules, compressed into tablets or filled into unit-dose sachets, the contents of which may be suspended in a liquid at a suitable pH immediately prior to use and drunk by the patient. Thus, the enteric-coated pellets may be taken orally as a suspension in a liquid (for example reconstituted as a suspension in a liquid at the time of use), preferably with food, or they may be packaged in tablets or capsules, for example of gelatin, which make the preparation easy to swallow but which disintegrate in the stomach, thus helping to mix the pellets evenly with food.

The composition of the coating should be optimised to maximise disintegration of the coating within the small intestine (duodenum, jejunum, ileum), preferably the duodenum, and to minimise the possibility of the coated microgranules/pellets passing through the small intestine, or even the whole gastrointestinal tract, intact. Preferably, drug is made bioavailable from the duodenum onwards.

Any coating can be used which ensures that the microgranules or capsules do not break up and release the drug until they are in the small intestine. The coating may be one which is pH-sensitive, redox-sensitive or sensitive to particular enzymes or bacteria, such that the coating only dissolves or finishes dissolving in the small intestine. Thus, the microgranules or capsules will not release the drug until they are in the small intestine.

The amount of the coating will typically be in the range of 4-20% w/w on dry granules, or 5 to 120% w/w of the weight of the dry granules

before the coating is applied. The amount of the particular coating used will be chosen according to the mechanism by which the coating is dissolved. Suitable amounts of coating for a capsule are well known to those skilled in the art.

Preferred coating materials are those which dissolve at a pH of 5 or above, for example pH 5.5 to 7.5, such as polyacids having a pK_a of 3 to 5. The coatings therefore only begin to dissolve when they have left the stomach and entered the small intestine. Such a coating can be made from a variety of polymers such as cellulose acetate trimellitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethyl ethylcellulose (CMEC) and shellac as described by Healy in his article "Enteric Coatings and Delayed Release" Chapter 7 in "Drug Delivery to the Gastrointestinal Tract", editors Hardy *et al*, Ellis Horwood, Chichester, 1989, or in Chapter 93 of Remington's: "The Science and Practice of Pharmacy", 19th Edition. PVAP is preferred to CAP or CAT, as it dissolves at a lower pH and hence ensures bioavailability from the duodenum onwards.

Other materials include methylmethacrylates or copolymers of methacrylic acid and methylmethacrylate. Such materials are available as Eudragit polymers (trademark) (Röhm Pharma, Darmstadt, Germany). Eudragits L, S, "L and S" and LD are anionic copolymers of methacrylic acid and methylmethacrylate and are generally suitable. For example Eudragit L100 (50% free carboxyl groups) or S100 (30% free carboxy groups) may be used. Eudragit L100-55 is especially suitable

and is obtained from L30 D-55 by spray-drying. It has equal amounts of methacrylic acid and ethyl acrylate and about 50% free carboxyl groups.

The pellets can also be given a sustained or controlled release property, should this be considered desirable, for example with waxes or silicone elastomers, especially by using melt granulation techniques.

A chelator of heavy metal ions, such as EDTA, can be included in a formulation of any aspect of the invention in order to prevent insoluble heavy metal ion salts or complexes of cromoglycate being formed. To be most effective, the chelating agent should be included in the granules or pellets but, alternatively, it can be mixed with the granules or pellets.

Suitable dosage regimes include the following. An initial daily dose of 1 mg to 2 g, preferably 100-1000 mg, more preferably about 200-800 mg, still more preferably about 300 to 500 mg is given in, for example, two divided doses spaced 12 hours apart. This may be increased at intervals of, say, 1-3 weeks, to a maximum of 1000-5000 mg daily. A typical maximum daily dose is 4000 mg or 100 mg/kg/day (whichever is the greater).

It is preferred that the daily dose is administered in the form of multiple tablets or capsules. For example, the daily dose may be administered as one table taken four times a day or as two tablets taken four times a day ie as eight tablets. This may have the benefit that sodium cromoglycate solution is released in the small intestine four or eight times during the day, respectively.

A further aspect of the invention provides a method of treating a patient for an allergic condition by orally administering a composition of the invention. The patient may first have been tested for serum IgE level and have been found to have a total level of at least 150 iu/ml.

Suitable IgE tests include an *in vitro* total IgE test and an *in vitro* specific IgE test, for example the UniCAP Total (or Specific) IgE tests sold by Pharmacia & Upjohn, which use the Allergen ImmunoCAPs as the allergen reagent.

We have found that it is probably necessary, and certainly desirable, for patients to be screened according to their IgE levels before treatment with sodium cromoglycate is undertaken. More specifically, we believe that patients with total serum IgE levels below 150 iu/ml are less likely to respond to the treatment. Although previous trials have measured IgE levels, the patients have not been selected for treatment according to the IgE level. This is one reason why we believe that the prior art studies have created the impression that sodium cromoglycate is not always effective in treating these allergic conditions.

Hence, according to a further aspect of the invention, a patient is selected for therapy according to whether their total serum IgE level is above 150 iu/ml. They may be tested immediately before therapy, or reference may be made to earlier test results.

The pathophysiology of food allergy and food allergic disease is unknown but we consider that the primary defect in a number of patients is an allergic inflammatory reaction in the mucosa of small intestine, in

particular the jejunum, caused by a reaction between specific substances in the food and specific IgE antibodies to that food produced by the patient. This allergic inflammatory reaction may cause symptoms itself but commonly does not. We consider that it results in an alteration in gut permeability allowing increased absorption of a number of substances, including those substances to which the patient is allergic. It is the increased absorption of these substances which causes secondary allergic reactions in secondary target organs, such as the skin in the case of atopic dermatitis and urticaria, the bronchial mucosa in the case of asthma, the nasal mucosa in the case of rhinitis and the colonic mucosa in the case of irritable bowel syndrome.

We further consider that the primary mode of action of orally administered sodium cromoglycate in the treatment of food allergy is to reduce the severity of the IgE-mediated allergic inflammatory reaction in the mucosa of the small intestine and therefore prevent the increased absorption of allergic substances. As the severity of the allergic reaction in the secondary target organs is related to the amount of allergen reaching the organ, this effect of the drug will be to reduce the severity of the allergic reaction in the secondary target organ.

It has recently been shown that an additional effect of sodium cromoglycate is to reduce the ability of IgE-producing cells, the B lymphocytes, to synthesise IgE antibody. It is proposed that the relevant B lymphocytes in the case of food allergy are found in the mucosa of the small intestine.

The present invention therefore provides a long-term treatment with oral sodium cromoglycate, based not only on its ability to reduce the consequences of the acute antigen/IgE antibody reaction but also the overall sensitivity by reducing the local synthesis of IgE antibody. This will initially be seen in the reduction in locally measured IgE antibody and ultimately in the amount of IgE antibody measured systemically, that is in the blood as Total Serum IgE.

The basis of an aspect of this invention is that the efficacy of oral sodium cromoglycate in the treatment of food allergic conditions will be increased by selecting patients who have clear evidence of an IgE mediated disease and whose clinical response is associated with a reduction in initially local and subsequently systemic levels of IgE antibody and secondly by increasing the bioavailability of the drug with a formulation that maximises the concentration of the drug in the secretions of the small intestine, in particular throughout the length of the jejunum.

Preferred aspects of the invention will now be described by way of reference to the following figures and non-limiting examples.

Figure 1: Dose response curve for efficacy of sodium cromoglycate on mucosa.

Figure 2: Relative concentrations of sodium cromoglycate achieved on the mucosa by different formulations.

Figure 3: Comparison of concentrations of sodium cromoglycate achieved in the stomach over time from a single dose of Nalcrom or Gastrofrenal.

Figure 4: Comparison of concentrations of sodium cromoglycate achieved in the stomach over time from a single dose of Nalcrom or Gastrofrenal.

Figure 5: Bioavailability of Nalcrom in the gut

Figure 6: Bioavailability of Altolyn(1) formulation in the gut

Figure 7: Bioavailability of Altolyn(2) formulation in the gut

Figure 8: Bioavailability of Altolyn(3) formulation in the gut

Figure 9: Bioavailability of Altolyn(4) formulation in the gut

Figure 10: Gastrointestinal tract

Figure 11: intragastric pH in six subjects followed over 24 hours over two consecutive days.

Figure 12: intragastric pH study in a larger group of healthy people who are eating solid food. Median hourly intragastric acidity (with 95% Cl) in 35 healthy female and 96 healthy male subjects. B,C,L,T,D,N = timing of meals. (Reproduced from Prewett *et al* 1991a).

Figure 13: Simultaneous quantification of postprandial volume of gastric contents (a), and its fraction being emptied into duodenum (b), which represents the actual gastric emptying rate (Malagelada *et al* (1976)).

Figure 14: Comparison between postprandial rates of gastric emptying of solids and liquids, in relation to the toatl volume of gastric contents. Note logarithmic scale on vertical axis (Malagelada (1977)).

Figure 15: Postprandial gastric emptying of various meal components (Malagelada (1977)).

Figure 16: Concentration (in mg %) of polyethylene glycol (C_{PEG}) in steak-meal supernate, stomach contents (sampled at 30 and 90 min after eating), and in intestinal fluid sampled at various distances from teeth. With intubation technique used, pylorus is at 60 cm, ligament of Treitz at 90 cm, and ileocecal valve at approximately 350 cm from teeth. Only 2 highest values of C_{PEG} obtained following each meal have been plotted (Fordtrans & Locklear (1966)).

Figure 7: Simultaneously measured postprandial volume being delivered into duodenum (____) and volume leaving duodenum at ligament of Treitz (- - -), with shaded area between these curves representing net volume change of duodenal chyme. Also plotted (. . . .) is portion of volume delivered into duodenum which represents meal volume rather than gastric secretions (Miller *et al* (1978)).

Example 1: granule formation (1)

The following solutions are made up:

Formulation A1, A2 or A3:

Formulation A1:

Water (purified)	1000 g	
Sodium Cromoglycate	150 g	)
		) solids 14.29%
Hydroxypropyl methyl cellulose	16.68 g	)
	1166.7 g	

Formulation A2: (for a larger and stronger granule)

Water (purified)	2000 g
Sodium Cromoglycate	300 g
Hydroxypropyl methyl cellulose	54 g
	2354 g

Formulation A3: (for an even stronger granule)

Water (purified)	2000 g
Hydroxypropylmethyl cellulose	222 g

2222 g

A 12% coat (solids) on 1000 g of granule at 11.27% solids requires 1065 g of suspension.

1000 g of powder Sodium Cromoglycate is placed into the bowl of an MPI Spray Granulator (Aeromatic-Fielder-UK) and fluidised using hot air at an inlet temperature of 70°C. The air rate used is approx 100 m^3/hr.

Once the material is fluidised and the powder bed has reached a temperature of 40°C, Formulation A1, A2 or A3 is sprayed through a two fluid nozzle placed above the fluidised bed, using atomizing air at approx 2 bar, to produce granules. The rate used is approx 27 g/min and therefore the time taken to spray 1167 g of solution is approx 44 minutes.

Once spraying has been completed the product is allowed to dry in the hot air stream until the bed temperature reaches 46°C. (The lowest bed temp reached is 35°C.)

If all the powder is collected, then the weight yield should be 1000 + the solution solids = <u>1166.7 g</u>.

However, the typical yields obtained were around 90%.

The granules may then be formed into tables with a disintegrant

Example 2: granule formation (2)

Granulation is necessary in order to improve flow and compression characteristics when preparing a dosage form, such as a tablet or capsule.

Wet granulation

Spray granulation in a fluid bed system is used to produce free flowing sodium cromoglycate granules:

Sodium cromoglycate is fluidised in the fluid bed with a diluent to aid fluidisation, for example microcrystalline cellulose. Onto the powder bed is sprayed a solution of binder and/or surfactant such as the amphoteric surfactant Miranol Ultra C32. The binder may be sodium cromoglycate, PVP, HPMC, PEG or other water soluble binder.

Water may be used without additional binder or surfactant. This is because of the limited solubility of the sodium cromoglycate (freely soluble up to 5% and soluble with difficulty up to 10%).

A chelating agent such as EDTA at 0.1% may be included.

The strength and size of the granules may be changed by varying the binder quantity and type. The binder may typically be used at about 10% (w:v) of the sodium cromoglycate.

The granule is dried in the same equipment, producing a free flowing material.

For a 500g batch size, typical conditions may be:
Inlet air temperature: 70°C
Bed temperature: 30°C to 40°C, typically 30°C to 35°C
Spray rate: 20-25g/minute
Air rate in fluid bed: 70-100 cubic metres/hour
Spray binder solutions typically have a solids contents w:w of 10-15%.

These conditions may require adjustment with changes in batch size.

The particle size of granules produced can be varied from 100 μm up to about 750μm. A suitable median particle size is about 200 μm.

Drying: the end point for drying may be assessed by measuring the temperature of the bed - as the granules become drier, the temperature of the bed rises. An end point bed temperature of 45-50°C gives a Loss on Drying (LOD) of 4.0-8.0%. LOD means the mass loss recorded after 20 minutes at 105°C in an infrared balance system. The granule can be run drier by setting the end point as 50-55°C bed temperature.

Dry granulation

Sodium cromoglycate may be granulated by roller compaction and the resulting granules put through a reducing mill and sized, as known to those in the art.

Wet or dry-formed granules produced as above (or granules produced as described in Example 1) are then combined with a disintegrant, for example microcrystalline cellulose and a suitable lubricant such as magnesium stearate to produce a compression mix which is subsequently tabletted.

A ratio of at least 2.5 parts microcrystalline cellulose to 1 part sodium cromoglycate granules may be required for fast tablet disintegration, for example 250mg microcrystalline cellulose to 100 mg sodium cromoglycate granules.

Tablets may typically contain 261 mg microcrystalline cellulose (for example, Avicel PH101 or Avicel PH102).

The final tablet weight for 100 mg active is 375mg. This may be tabletted on an 11mm double radius normal concave tablet punch and punched to a hardness of between 4 and 10 kilograms (the term used in the art, which may correspond to kilograms per cm^2).

The tablet may be enteric coated using a fluid bed based coating system or using the coating pan technique in a side vented pan.

Shuteric (polyvinyl acetate phthalate) or Eudragit, Aquacoat, Aqoat or Aquateric may be used as the enteric coating. The tablets are coated to a level of 5 to 20%, usually 10 to 15%, particularly 12%.

Filling into capsules

Alternatively, an appropriate fill of sodium cromoglycate and disintegrant, for example 100 or 200 mg sodium cromoglycate per capsule, is weighed into hard gelatin capsules, and the capsules sealed and enteric coated in a fluidised spray coater or rotary coating pan. The fill may comprise granules comprising sodium cromoglycate and disintegrant, for example microcrystalline cellulose and optionally an amphoteric surfactant, for example Miranol Ultra C32. The ratio of disintegrant to sodium cromoglycate in the granules may be more than 1.5:1w:w, preferably 2.5:1.

Example 3: granulation - high shear mixer method

An alternative method involves the use of high shear mixer technology using a melt granulation technique.

Stage one - this process involves mixing SCG with a melt binder such as PEG under ambient conditions. The mixture is then heated to the melt point of the binder (approx 60°C) in a high shear mixer and mixed intensely to produce a round particle of approximate size 200 to 500 μm, and then cooled.

Stage two - these particles are then enteric-coated in a fluid bed spray coater (obtainable from Aeromatic-Fielder Ltd, Hampshire, UK) with AQOAT (Shin-Etsu), Aquateric (cellulose acetate phthalate aqueous redispersible powder and a suitable plasticizer, for example diethyl phthalate (DEP); FMC Corporation, Pharmaceutical Division, 1735 Market Street, Philadelphia, PA 19103) or one of the other

commercially available coatings such as a CAP (FMC), CAT (Eastman Kodak), PVAP (Colorcon), or a Eudragit (Röhm Pharma).

Enteric coating the individual granules

1000 g of the above produced granules are now transferred to the bowl of a fluid bed coater such as an MPI Precision Coater, which uses an upspray system for spraying a coating solution/suspension on to the fluidised granules.

The atomizing air pressure is approx 3 bar.

The bed of granules is preheated to a temperature of approx 36°C (inlet air temperature of 60°C used) before spraying commences.

The coating solution (Formulation B) is sprayed onto the granules at an approx rate of 18 g/min using atomizing air pressure of approx 3 bar and therefore the time taken to spray 1065 g of solution is approx 60 mins (1 hour). During the coating the temperature of the granules gradually drops and by the end has reached approx 25°C. Once all the coat has been added the bed is allowed to heat up to approx 40°C before stopping the process to allow the coat to dry. Total process time including drying is approx 1½ hours (90 mins). In nearly all cases/batches produced to date the yields have been very good at 100%.

Coating Suspension

Formulation B:	%		for 1000 g of granule
Aqoat HPMC-AS-LF	7.0	)	74.55

Triethyl Citrate	1.96	)	20.87
Talcum Powder	1.1	) 11.27%	11.72
Titanium Dioxide	1.0	) solids	10.65
Sodium Lauryl Sulphate	0.21	)	2.24
Purified Water	88.73	)	944.97
	100.00		1065 g

Finally, the coated granules are filled into capsules for the final dosage form.

Stage three - these coated particles may then be used to produce a variety of oral dosage forms such as capsules to be swallowed, or tablets to be swallowed, or filled into unit-dose sachets the contents of which may be suspended in a liquid of suitable pH immediately prior to use and drunk, or partially filled into bottles to which a suitable diluent is added, by the pharmacist immediately prior to it being dispensed, and drunk.

Example 4

Patients with symptoms of food allergy or chronic disease such as irritable bowel syndrome, rhinitis, asthma, conjunctivitis, atopic dermatitis, urticaria, migraine, eczema or hyperactivity in which allergy to foods has been shown to be a causative factor are investigated for total serum IgE levels by the Pharmacia & Upjohn UniCAP Total IgE Test, and preferably also investigated for sensitivity to food or drink by the Pharmacia & Upjohn UniCAP Specific IgE Test and/or skin prick tests to ingested allergens. If total serum IgE levels are above 150 iu/ml

or if a skin prick test or UniCAP Specific IgE test is positive the patient should be considered for treatment with the formulation of the invention.

Adults and children over 12 years of age should be started on a daily dose of from 400 mg a day taken before food in two divided doses, for example at 8.00 am and 8.00 pm. Capsules or tablets should be swallowed whole with water, not milk, milkshake, fruit juice or other potentially allergic foodstuff.

Children between the ages of 12 and 5 years should be started on a daily dose of from 200 mg a day taken before food in two divided doses, for example at 8.00 am and 8.00 pm. Capsules should be swallowed as above.

Children below 5 years of age should be started on a daily dose of from 50 to 100 mg a day taken before food in two divided doses, for example at 8.00 am and 8.00 pm. Capsules should be swallowed as above.

Patients may initially experience a worsening of symptoms. This is a positive sign that the medication is having an effect. In these patients the dosage should be reduced to half for 1 week before being increased again. Alternatively an anticholinergic drug such as dicyclomine hydrochloride or propantheline bromide may be administered concurrently for the first week.

After 4 weeks another serum IgE measurement should be taken. If this is lower it may indicate that the patient is responding even if there is no symptomatic improvement.

Serum IgE measurements should continue to be taken at monthly intervals for 6 months, 3 monthly for a further 6 months and 6 monthly thereafter. A maintained reduction in levels will indicate a reduction in sensitivity to the ingested allergens and symptomatic improvement in the condition.

It is important that patients continue to take their medication even though their symptoms are absent or significantly improved. If they do not, their IgE levels will begin to increase again and when they start the medication again it will take time for the IgE levels and therefore the symptoms to subside - but patients will not wait and will conclude that the medication is ineffective.

Example 5: factors affecting the clinical efficacy of sodium cromoglycate

Sodium cromoglycate may have a bell-shaped dose response curve or S-shaped dose response curve (Figure 1). In either case it means that if a sufficient concentration of drug is not present the desired clinical effect will not be achieved.

Most solutions of sodium cromoglycate (Rynacrom, Lomusol, Opticrom and Intal nebuliser solution are used at a concentration of 2%, suggesting that this is an effective dose.
The clinical effect of sodium cromoglycate is dependent not only on dose but also on the temporal consistency and evenness of the application of the drug to the appropriate mucosal surface. It is also preferably to

exclude to the maximum extent possible heavy metal or alkaline earth ions.

Concentrations of sodium cromoglycate achieved by Nalcrom in the small intestine (based on a simplified model of gut fluid dynamics).

Based on the following assumptions:

The drug is water soluble, poorly absorbed (1-2%), not adsorbed to food particles or gastric mucosa, acid insoluble (pKA 2), lipid insoluble.

In a day, the average stomach passes 8 litres (6mls/min) and the average volume of fluid contained in the stomach is 100 mls.

A complete analysis requires consideration of several factors which will determine the drug's concentration in the upper duodenum. These factors have not been considered in the calculations shown below.

The concentration of a drug in the upper part of the duodenum will depend on many factors of which the major ones are listed below.

Concentrations in the first part of the duodenum are essentially going to be related to gastric physiology and the physicochemical properties of the drug. Beyond the first part of the duodenum then pancreatic and biliary secretion will become important, as will absorption both of the drug and of the meal contents. Superimposed on this will be wide individual variation and probably within individuals, depending on their lifestyle at the time they are taking the drug, exercise, etc.

Factors include:

timing of dosage in relation to meals (gastric pH problems)
volume of meals and composition
gastric emptying patterns (dependent on amount of fat, osmolarity)
absorption of the drug
rate of transit through duodenum and small intestine
chemical nature of the drug and its physical properties
amount of salivary, pancreatic and biliary secretion (mid-duodenum)

If, for example, a patient is pre-dosed with sodium cromoglycate and then, 15 minutes later, challenged with food (approximately 90ml volume), then the total volume diluting the sodium cromoglycate during that time is 100ml (stomach contents) + 90 ml (meal volume) = 190 ml.

The concentration of sodium cromoglycate leaving the stomach may be (dose (g) x 100/190 ml)% (w:v).
Therefore, if the dose is 800mg, the concentration is 0.42%, for 400mg, 0.21%, for 200mg, 0.11%, and for 100mg, 0.5%.

However, this concentration of sodium cromoglycate is very unlikely to be bioavailable if it has been exposed to gastric fluid as it is insoluble in an acid medium and may not dissolve even on entering a less acid medium (as discussed elsewhere and shown in Figure 5).

Nalcrom is presented as a capsule from which a drink is prepared by pulling the capsule apart and dissolving the contents in hot water, followed by dilution with cold water. Alternatively, Nalcron (France)

and Lomudal Gastrointestinal (Scandinavia) are presented as 2% solution in an ampoule, the contents of which are drunk.

For a Nalcrom dose, the concentration of the solution as drunk is 0.2g in 50 ml ie 0.4%.(w:v). The concentration (probably not in solution) in the stomach after dosing may be 0.13% (0.2g/150 ml).

After 4 hours, 1300 ml of fluid may have passed through the stomach, so the concentration in the stomach (probably not in solution) at this time may be 0.2g/1300 ml ie 0.015%(w:v).

Concentration of sodium cromoglycate achieved by Gastrofrenal in the stomach.

Gastrofrenal is presented as a powder of sodium cromoglycate mixed with 5 g of sugar in a sachet. The contents of the sachet are poured into a glass, water added and the solution/suspension drunk.

500 mg is delivered in 140 ml to the stomach, so the initial concentration may be 0.5g/240 ml ie 0.2%.

[How is Gastrofrenal formulated? Is it delivered to the stomach or the small intestine?]

Altolyn - a formulation of the invention comprising disintegrant.

A tablet formulation may release 100 mg of sodium cromoglycate in a rapid burst early in the small intestine.

If an aliquot of 150 ml travels through the pyloric sphincter with a tablet containing 100 mg sodium cromoglycate, this provides 0.1g/150 ml ie 0.06% (w:v). For a tablet containing 200 mg sodium cromoglycate, this provided 0.2g/150 ml ie 0.13% (w:v).

If an aliquot of 111 ml travels through the pyloric sphincter (8 litres/24 hr = 111 ml/20 min), then the concentrations achieved will be 0.09% and 0.18% (w:v) respectively.

The burst is triggered by the enteric coating on the tablet dissolving rapidly as soon as it reaches alkaline conditions. The liquid then reaches the inner core of the tablet and causes the disintegrant combined with the sodium cromoglycate to swell and disperse the active ingredient very quickly.

The tablet may also contain a chelating agent to ensure the maximum dose of cromoglycate is maintained as the sodium salt (ie is not precipitated out as an insoluble salt).

The preferred dosage of the formulation may be 2 tablets eight times a day, so that a burst of sodium cromoglycate is released in the small intestine 8 time during the day.

Formulation of sodium cromoglycate is difficult because the physical properties of sodium cromoglycate are unusual. In other tablet formulations of sodium cromoglycate, the sodium cromoglycate immediately forms a glutinous gel which seals the drug preventing

further wetting. The use of a disintegrant in an enteric coated tablet formulation may be necessary for the sodium cromoglycate to disperse rapidly in the small intestine.

Example 6: calculations concerning concentration of a drug in the upper duodenum

The following calculations may apply to sodium cromoglycate and to other drugs.

Assumptions:

The drug is water soluble

Poorly absorbed (1-2%)

Acid insoluble (PKA 3.5 to 2.0)

Dose 200 mg to adults before meals and 100 mg to children in 30-50 mls water

A burst release dosage form is considered

Factors which will determine the drug's concentration in the upper duodenum:

The concentration of a drug in the upper part of the duodenum will depend on many factors of which the major ones are listed below. Concentrations in the first part of the duodenum are essentially going to be related to gastric physiology and the physicochemical properties of the drug. Beyond the first part of the duodenum then pancreatic and biliary secretion will become important, as will absorption both of the drug and of the meal contents. Superimposed on this, will be wide

individual variation and probably within individuals, depending on their lifestyle at the time they are taking the drug, exercise, etc, etc.

Factors include:
timing of dosage in relation to meals (gastric pH problems)
volume of meals and composition
gastric emptying patterns (amount of fat, osmolarity)
absorption of the drug
rate of transit through duodenum and small intestine
chemical nature of the drug and its physical properties
amount of salivary, pancreatic and biliary secretion (mid-duodenum)

In trying to estimate possible concentrations of the drug in the stomach and, therefore, upper duodenum the following assumptions have been made:

the drug is not absorbed to food particles or gastric mucosa
not absorbed significantly from any part of the gut
totally soluble in water but not in lipid
does not form a gel or colloidal solution

Gastric pH and the timing of drug delivery

Fig 11 shows intragastric pH in six subjects followed over 24 hours over two consecutive days during which time they ate standardised meals, (the nature of which is not given in the paper by Fimmel *et al*). It will be noted that gastric pH frequently falls to between 1 and 2 and that first thing in the morning before a breakfast meal it is invariably at this level.

Fig 12 shows the results of a similar study in a larger group of healthy people who are eating solid food. Intragastric acidity for much of the day lies between 100mmol/L and 10 mmol/L (pH1-pH2) and only after meals rises to pH in the region of 4-5.

The significance of this for a drug which is insoluble in acid and will therefore be only 5% dissociated at pH 2.5 needs to be considered. It would seem likely that the drug taken on an empty stomach before breakfast or before the main meals during the day would enter an acid milieu and precipitate.

If the drug were taken into a pH-neutral stomach in the fasting state in a volume of 50ml water, intragastric concentration would be between 1.5 and 2.5 g/L (0.15-0.25%w:v) since fasting gastric content are usually between 30-80 ml.

Gastric concentration following meals

Concentration of the drug in the first part of the duodenum will depend very largely on its concentration in the stomach and the rate of gastric emptying.

Fig 13 shows the volume of gastric contents after a 400 ml meal comprising steak, bread, butter, ice-cream, chocolate syrup and water. The volume of gastric contents is around 400 ml at 30 min, remains at this level for about one hour and then decreases linerally. Fig 13b

however shows that gastric emptying of liquid is logarithmic in form and this has been shown in many studies.

Fig 14 shows that liquids and solids in a test steak meal empty at different rates, with solid emptying more erratically depending on their nature.

Fig 15 shows that gastric secretion itself makes a major contribution to intragastric volume during gastric emptying. Digestion and emptying is usually complete in 4 hours.

Using these data it is possible to make some approximately calculations as to concentration of a water soluble drug in gastric content at intervals after the meal, taking account of

- a meal volume of 400 ml
- the dosage of the drug in 50 ml
- gastric emptying
- gastric secretory rates as indicated

Fig 15 shows that the proportion of material leaving the stomach is very much influenced by the volume of gastric secretion. Immediately after the meal, say at 15 min, gastric secretion will be about 25% of the total volume of gastric contents. The approximately concentration of the drug would therefore be (for a gastric volume of 562.5 ml) 355 mg/L (0.0355% w:v). This is likely to be its maximum concentration in the stomach and therefore in the first part of the duodenum at any stage. By

30 min the concentration of the drug would fall to around 200 mg/L and at one hour less than 100 mg/L thereby progressively declining to zero at 3-4 hours. During these studies, reported by Malagelada *et al* in 1976, gastric pH started at 2, rose to a maximum of approximately 5, and was back to 2 within 1-2 hours of the meal being eaten. These pH effects need to be considered.

In the now classical studies of Fordtran & Locklear published in 1966, an inert marker was added to two separate test meals and its concentration in stomach, duodenum and small intestine measured over several hours in small number of healthy subjects. The meals either contained steak and were of a volume of 645 ml or a milk meal of about 315 ml.

Fig 16 shows marker concentration (polyethylene glycol) in aspirates from various parts of the stomach at 30 and 90 min after eating. Using the ratios of PEG in the test meal, and in the stomach at various times, it is possible to calculate the concentration of a water soluble drug. In the stomach at 30 min this would be 160 mg/L and at 90 min 51 mg/L.

Fig 17 shows the changes in the volume and composition of material delivered to the duodenum and at the ligament of Treitz following a similar 400 mg steak meal used in previous studies. Using this and data from Johnansson and colleagues (1976) which showed that the fractional elimination rates of liquid meals from the stomach is between 34-61% per 20 min, it is possible to make some estimates of mid and lower duodenal and upper jejunal concentrations of drug following standard meals. Using Fordtran & Locklear's data, drug concentration in the

mid-duodenum, where meal volume was estimated to be 1.5L postprandially, would be 133 mg/L but in the upper jejunum this would have increased to 266 mg/L because of net absorption of fluid. Miller *et al*'s studies show that the volume of material passing the ligament of Treitz is greater than that entering the duodenum because of pancreatic and biliary secretion. Initial concentrations of a drug at the ligament of Treitz therefore immediately following a meal will be about one third of that of the concentration of the drug entering the duodenum.

Conclusions

Predicting the concentration of a drug in the upper duodenum requires many assumptions to be made and cannot be done with accuracy. The only reliable way to get the information would be to put a tube into the duodenum and sample following meals of different composition. Gastric emptying is a key factor as is the volume and composition of a meal. Gastric emptying will of course be influenced by a number of other factors unrelating to the meal such as age, presence of diabetes, drug, etc.

Perhaps the most important determinant of the drug's concentration, apart from its does and solubility, will be the volume of the meal in which it is taken and the pattern of gastric emptying . With an average meal comprising at least 400 g and gastric secretion during the course of digestion comprising twice that volume, the concentration of the drug will never be greater than its concentration in the initial meal if taken during eating, and will rapidly decline due to gastric emptying and intestinal secretion thereafter. Concentrations would likely be less than

10% of the original concentrations in the stomach by 2 hours and would be undetectable at 4 hours.

Solubility in acid is also a key problem.

Dry concentrations in children would be approximately half those in adults if the dose was 100 mg per meal - unless dealing with very small children, say under 5 years.

Concentration in the duodenum and jejunum following "burst release" in the duodenum would be critically dependent on the dry release properties of the drug in the gut.

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CLAIMS

1. An oral drug delivery composition comprising a chromone wherein the chromone is made bioavailable in the small intestine following human oral administration, characterised in that the chromone is made bioavailable within 10 minutes of exposure of the composition to simulated intestinal fluid.

2. A composition according to claim 1 wherein the composition further comprises disintegrant at a ratio of at least 1.5:1(w:w) of disintegrant to chromone.

3. A composition according to claim 1 wherein the composition comprises substantially spherical pellets of up to 5 mm diameter, each pellet having an enteric coating.

4. An oral drug delivery composition comprising a chromone wherein the composition further comprises disintegrant at a ratio of at least 1.5:1(w:w) of disintegrant to chromone.

5. An oral drug delivery composition comprising a chromone, wherein the composition comprises substantially spherical pellets of up to 5 mm diameter, each pellet having an enteric coating.

6. A composition according to any one of claims 1 to 5 wherein the composition further comprises an amphoteric surfactant.

7. An oral drug delivery comprising a chromone, wherein the composition further comprises an amphoteric surfactant.

8. A composition according to any one of claims 2, 4 or 6 wherein the ratio of disintegrant to chromone is at least 2.5:1.

9. A composition according to any one of claims 2, 4, 6 or 8 wherein the disintegrant is microcrystalline cellulose.

10. A composition according to any one of claims 2, 4, 6, 8 or 9 wherein the composition is formulated as a tablet.

11. A composition according to claim 3 or 5 wherein the pellets are melt pellets.

12. A composition according to any one of claims 3, 5 or 11 wherein the pellets have a diameter of between 0.7mm and 1.8 mm.

13. A composition according to any one of Claims 3, 5, 11 or 12 wherein the pellets are packaged in one or more capsules formed of a material which will release the microgranules in the stomach.

14. A composition according to any one of the preceding claims additionally comprising a chelator of heavy metal ions, such as EDTA.

15. A composition according to any one of the preceding claims wherein the chromone is sodium cromoglycate.

16. A method of treating a patient for an allergic condition comprising administering to the patient a composition according to any one of the preceding claims.

17. A method according to Claim 16 wherein a daily dose of 100-5000 mg is delivered.

18. A method according to claim 16 or 17 characterised in that the patient has first been selected to have a total serum IgE level of at least 150 iu/ml.

19. A method according to Claim 18 wherein the serum IgE level of the patient is tested during the course of the treatment and the dose of chromone is increased or prolonged if the level has not fallen to, or is not falling towards, 150 iu/ml.

20. A method according to any one of Claims 16 to 19 wherein the patient is also given anti-muscarinic medication so that at least part of the effect of the chromone treatment overlaps temporally with at least part of the effect of the anti-muscarinic treatment.

21. A composition according to any one of claims 1 to 15 for use in medicine.

22. Use of a composition according to any one of claims 1 to 15 in the manufacture of a medicament for treating a patient with an allergic condition.

23. Use of an amphoteric surfactant in the manufacture of a medicament for treating a patient with an allergic condition wherein the medicament is administered orally.

ABSTRACT

Treatment of allergic conditions

Orally administered sodium cromoglycate has been found to be effective in the treatment of allergic conditions such as asthma, general food allergies, ulcerative colitis, atopic eczema, chronic urticaria and irritable bowel syndrome if it is presented such that the sodium cromoglycate becomes bioavailable within 10 minutes of exposure to intestinal fluid. The sodium cromoglycate may be presented as individually enteric-coated pellets or microgranules packaged with disintegrant in a ratio of at least 1.5:1 disintegrant:sodium cromoglycate (w:w). Optionally, the patients are first selected to have a total serum IgE level of at least 150 iu/ml.

Figure 1

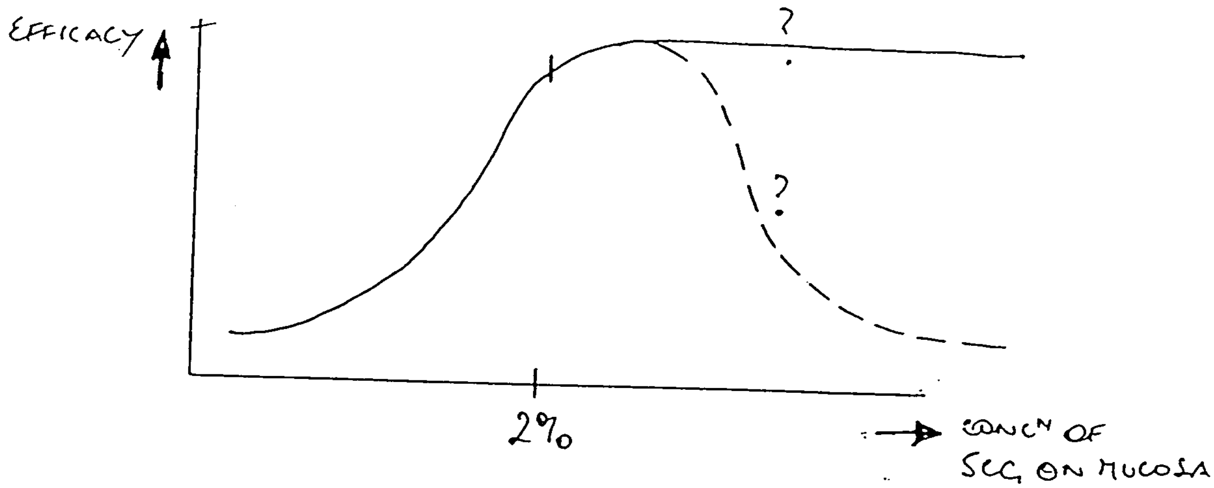

Figure 1

Relative concentrations on the mucosa of a range of Sodium Cromoglycate solutions

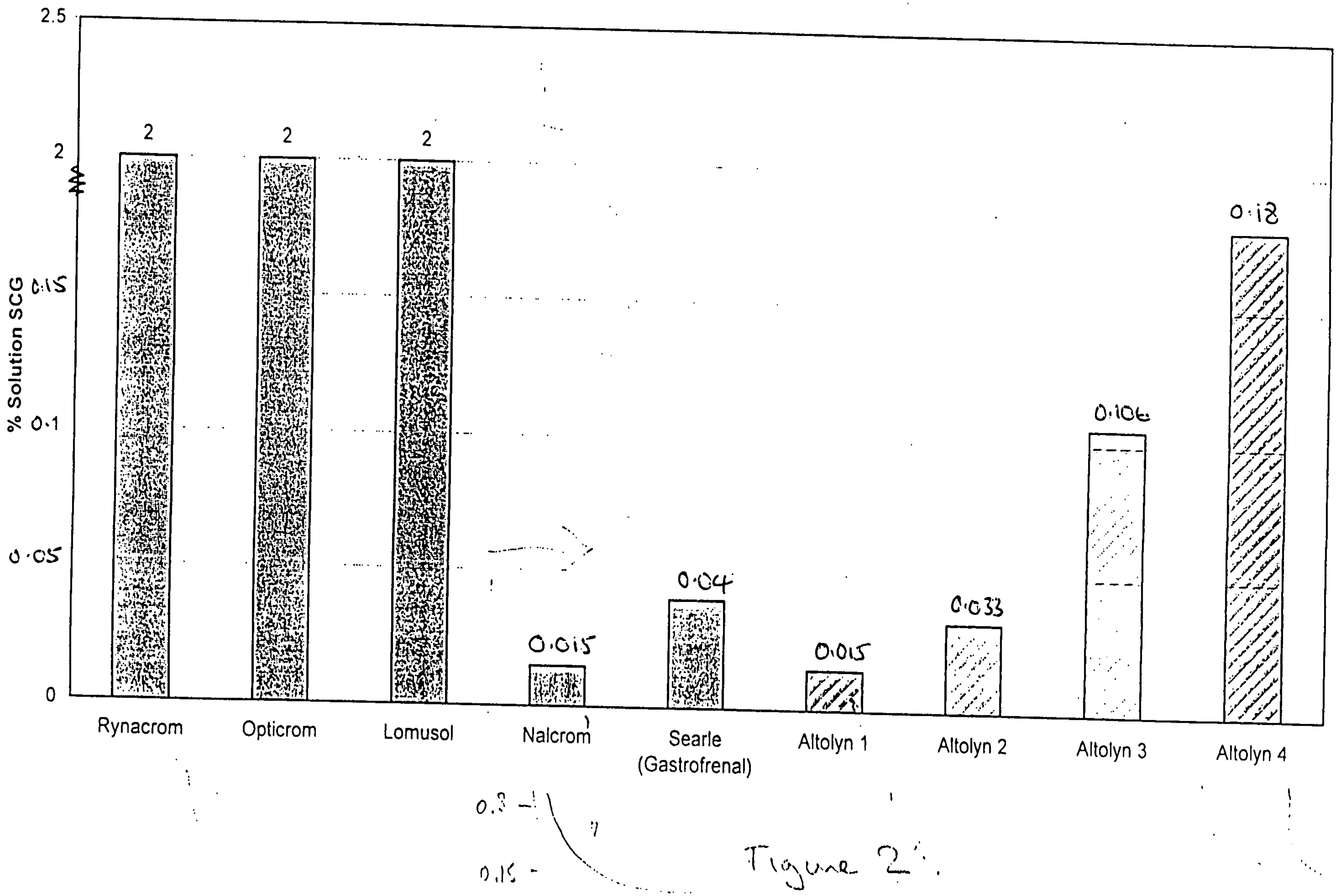

Figure 2

200mg Nalcrom and 500mg Gastrofrenal dilution in the stomach over time from a single dose

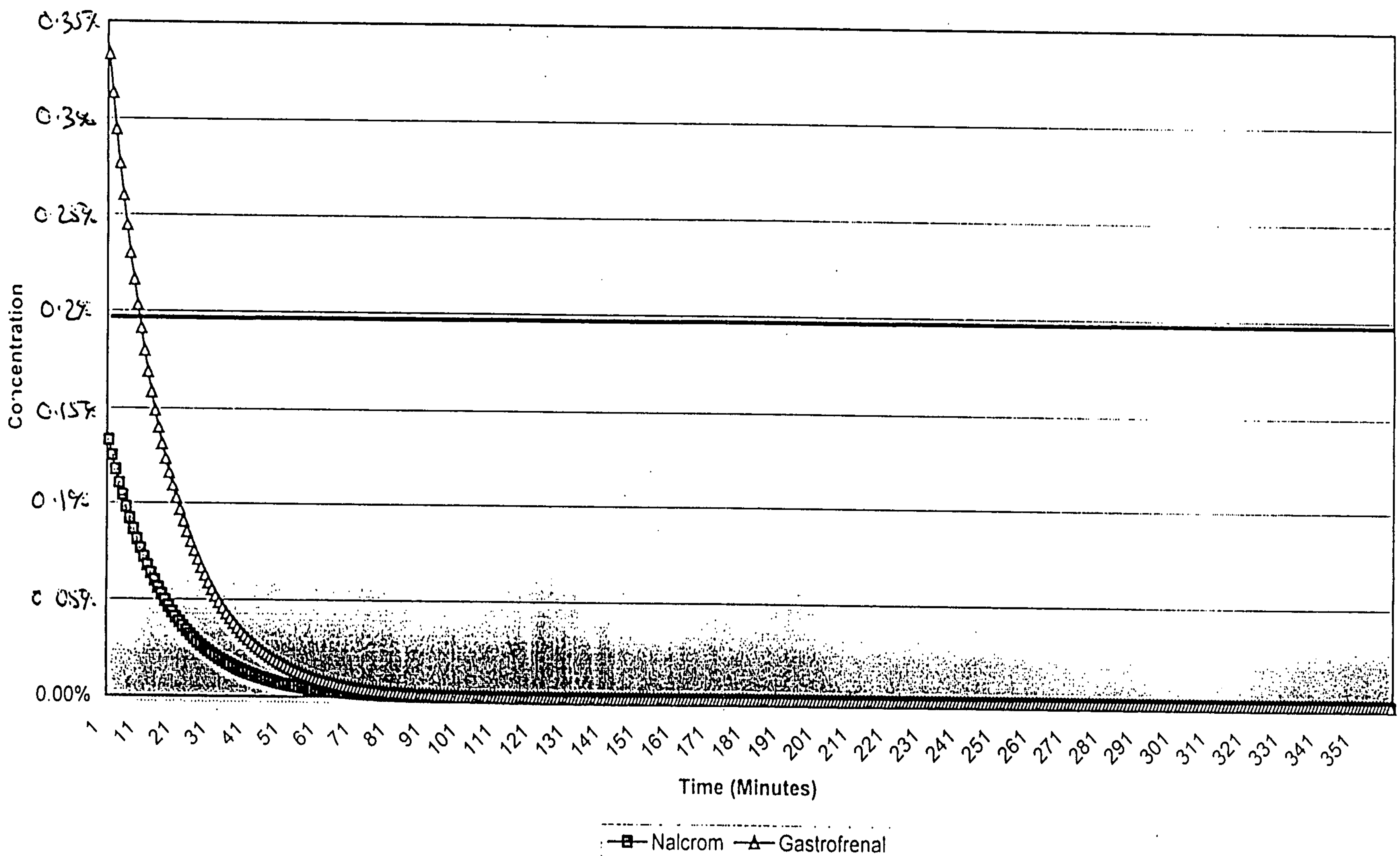

Figure 2

200mg Nalcrom and 500mg Gastrofrenal dilution in the stomach over time from a single dose

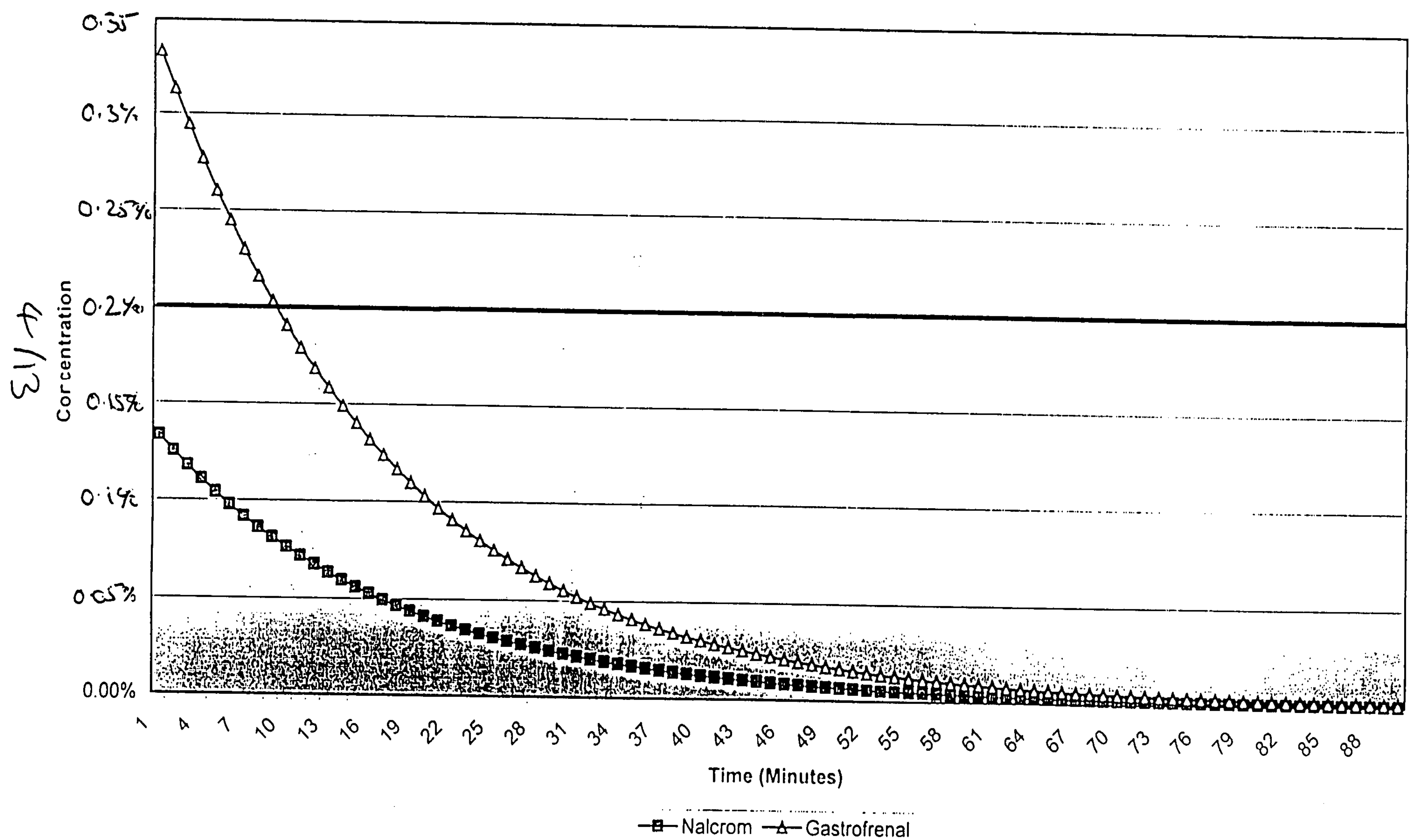

Figure 4

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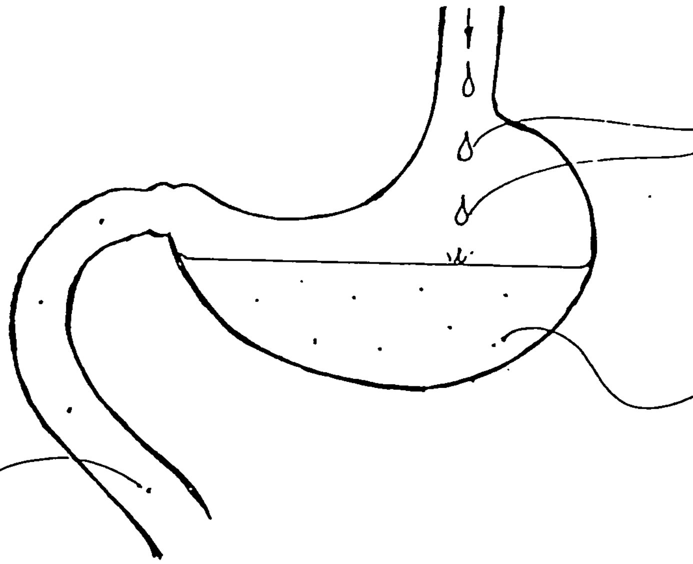
Figure 5

NALCROM - EXISTING PRODUCT

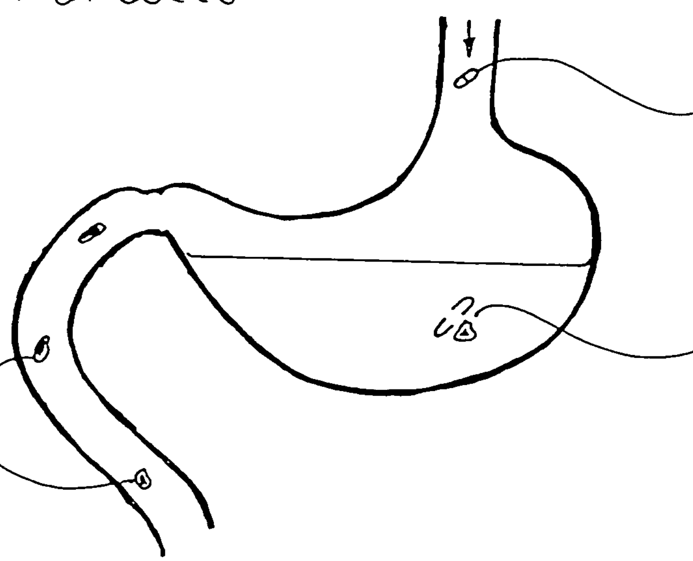


DILUTE SOLUTION
OF SCG
(4% SOLUTION)

VERY DILUTE
SOLUTION OF SCG
(0% IN ACID MEDIUM)

VERY VERY
DILUTE
SOLUTION
OF SCG
(< 0.015% SOLUTION)

OR NALCROM CAPSULES



2 CAPSULES OF EXISTING
PRODUCT SWALLOWED
100mg × 2 = 200mg.

CAPSULE DISSOLVES
RELEASING SCG.
A GEL FORMS AROUND
POWDER SEALING THE
BULK OF UNWETTED
POWDER INSIDE
(0% IN ACID MEDIUM)

SEALED
LUMP OF
SCG TRAVELS
THROUGH THE
DUODENUM -
RELEASING SCG
SLOWLY AND
UNEVENLY.

LOW CONCENTRATION (0.026%)
EFFECTIVELY SUSTAINED RELEASE

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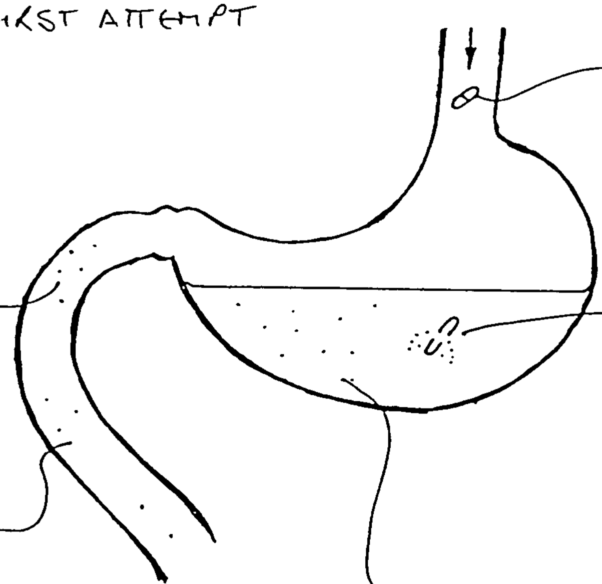
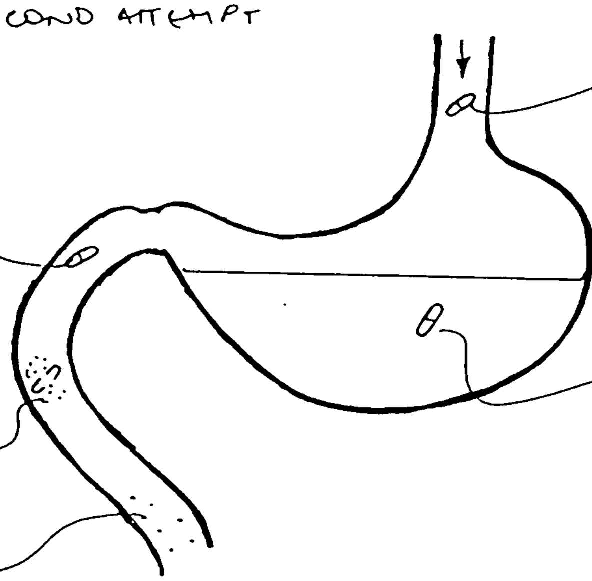
Figure 6

ALTOLYN - FIRST ATTEMPT



(*1) CALCULATED AT 0·015 -0·02 % SOLUTION

ALTOLYN - SECOND ATTEMPT



MUCH BETTER CONCENTRATION (*2) BUT SLOW RELEASE (40 MINS). SOME CLUMPING STILL. CAPSULE THE PROBLEM

(*2) CALCULATED AT 0.033% SOLUTION

Figure 7

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Figure 8

ALTOLYN - THIRD ATTEMPT

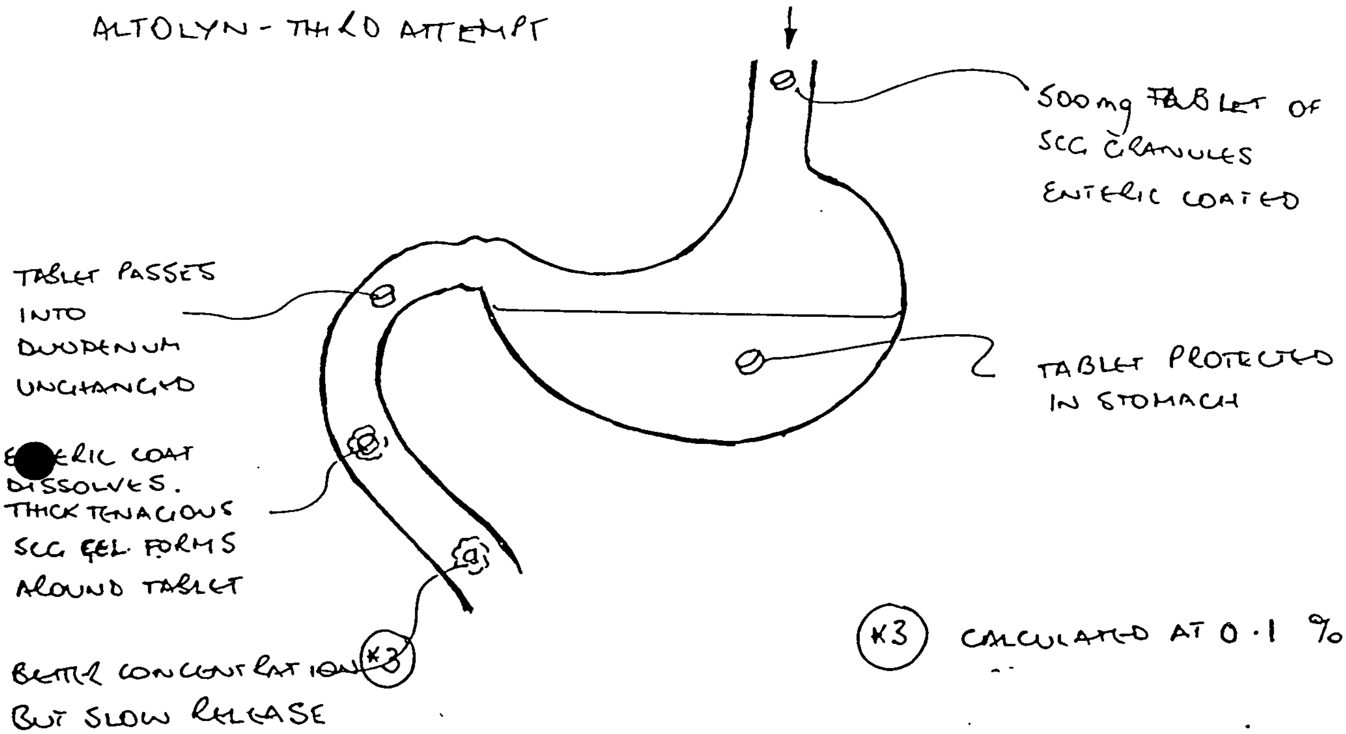
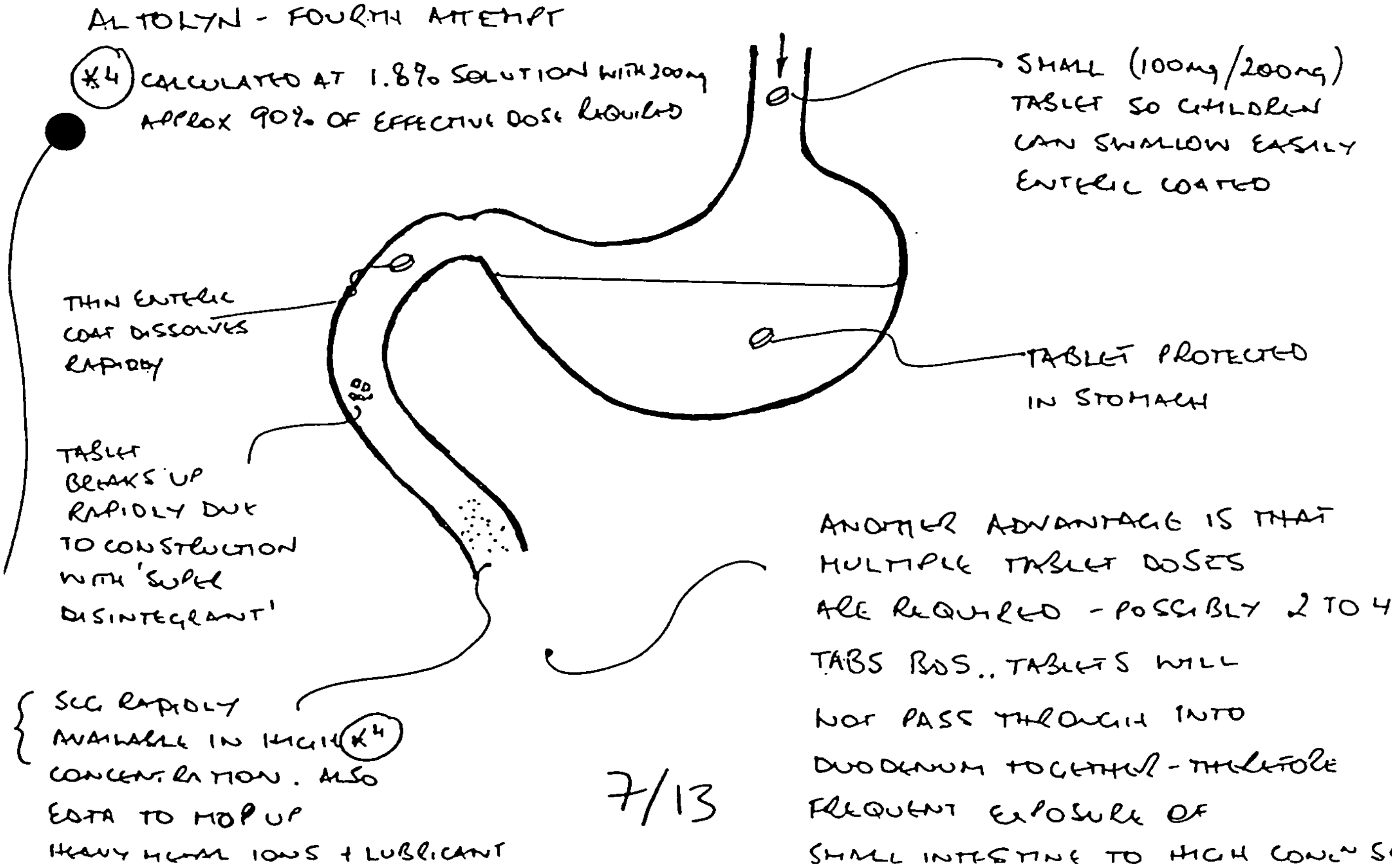


Figure 9.

ALTOLYN - FOURTH ATTEMPT

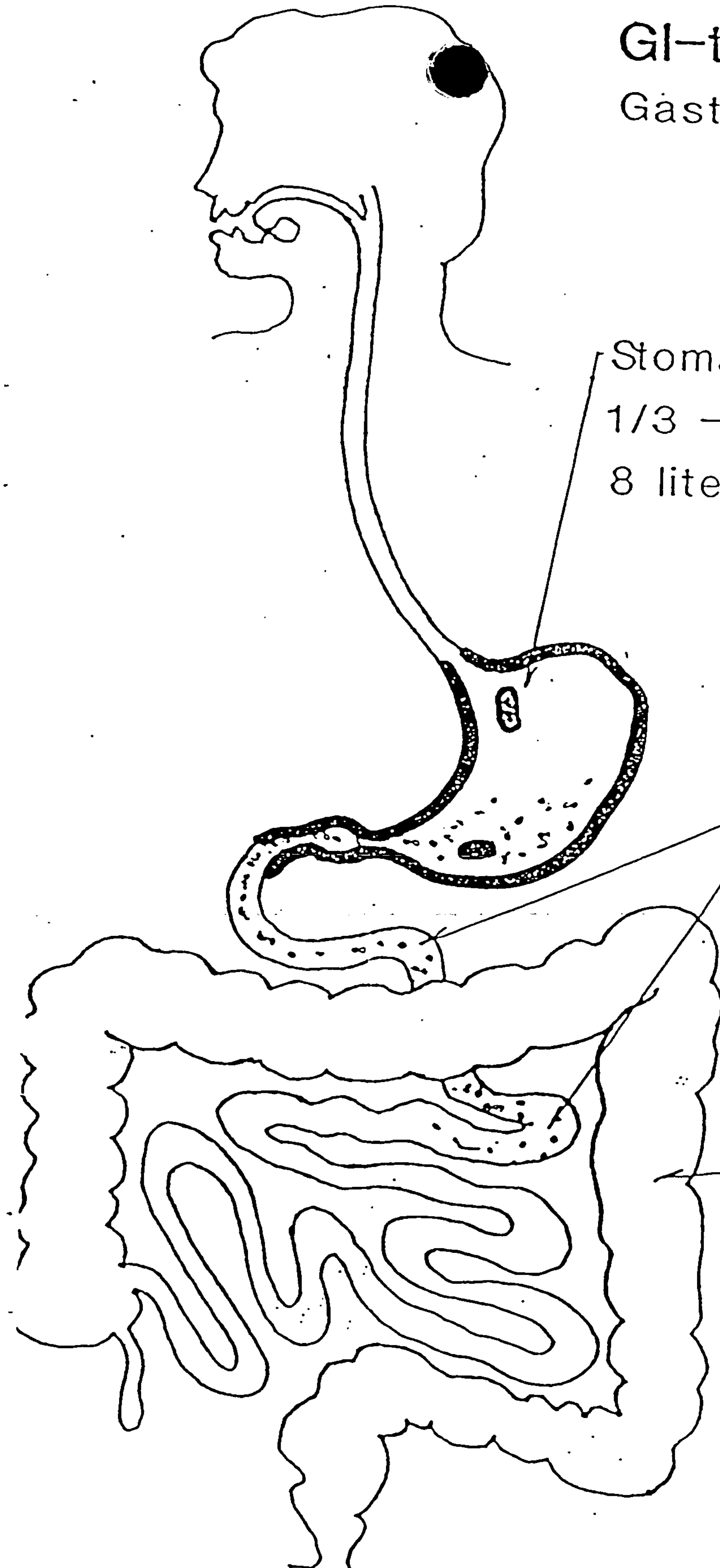
(*4) CALCULATED AT 1.8% SOLUTION WITH 200mg
APPROX 90% OF EFFECTIVE DOSE REQUIRED



GI-tract

Aeromatic-Fielder Ltd.

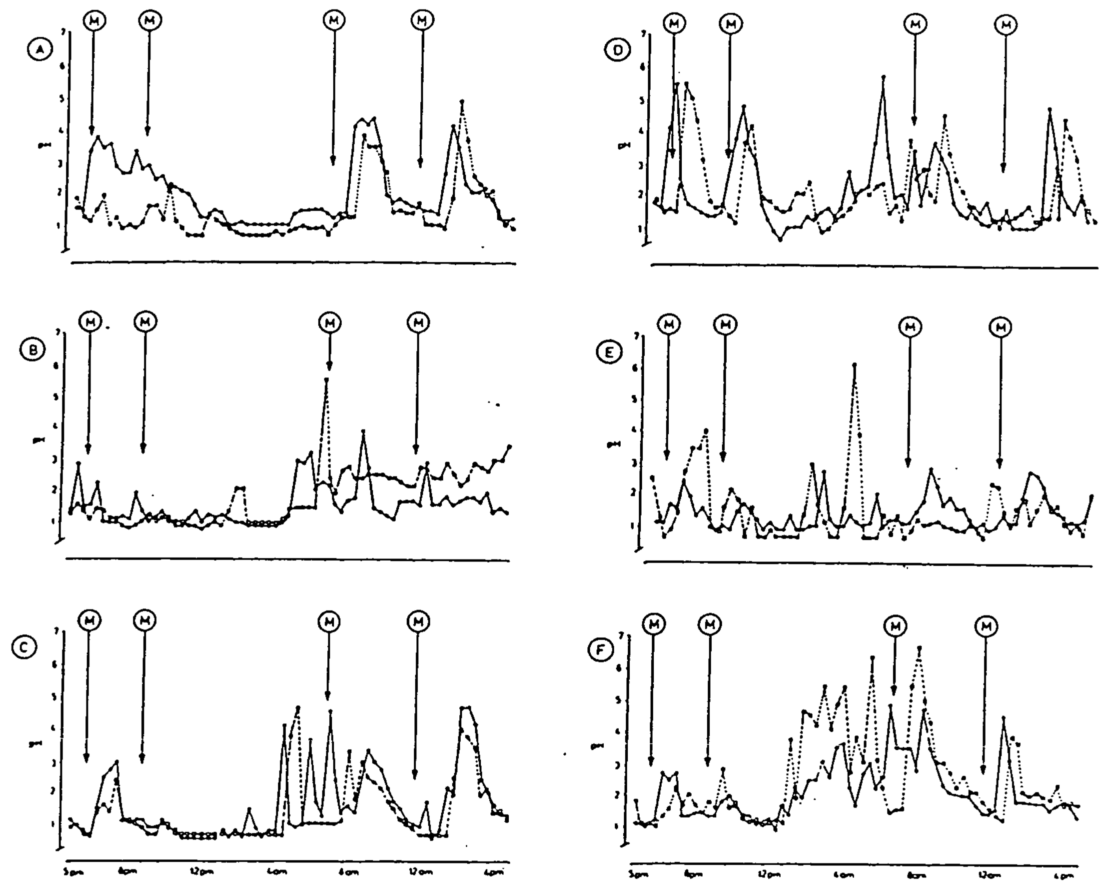
Gastro-intestinal tract



GEA
Process Technology Division

Figure 10   8/13

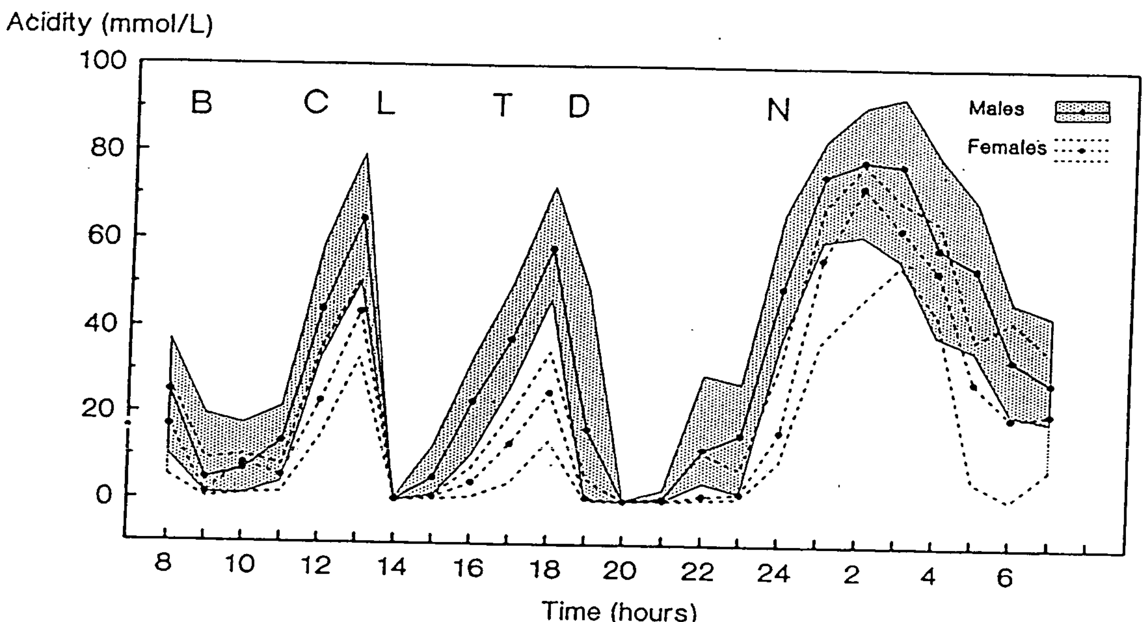
Fig. 11



Reproducibility of two consecutive 24-h pH-metries. Panels A to F show the two pH curves of each subject on day 1 (*closed circles*) and 2 (*open circles*). Each point represents mean pH value of 10 min. Duration of each test from 5 PM to 5 PM. Standardized meals (*M*) were taken at ~6 PM, 9:30 PM, 7:30 AM, and 12:30 PM.

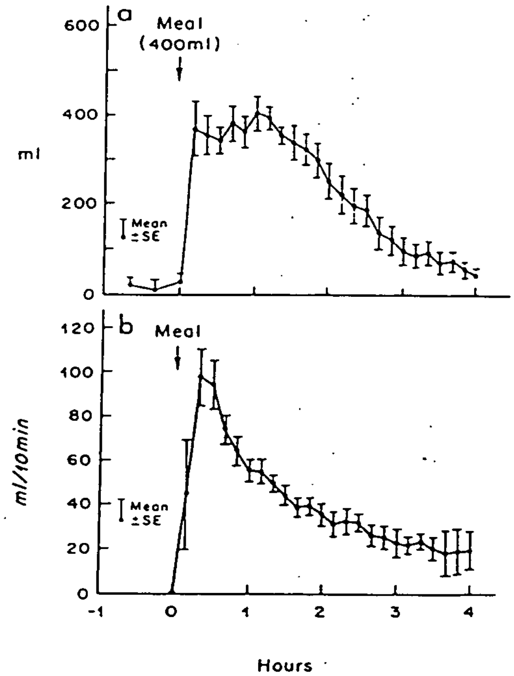
Fimmel et al 1985

Fig. 12



Median hourly intragastric acidity (with 95% CI) in 35 healthy female and 96 healthy male subjects. (For key to symbols B, C, L, T, D, N, see Fig. 3.10. Reproduced, with permission, from Prewett et al 1991a).

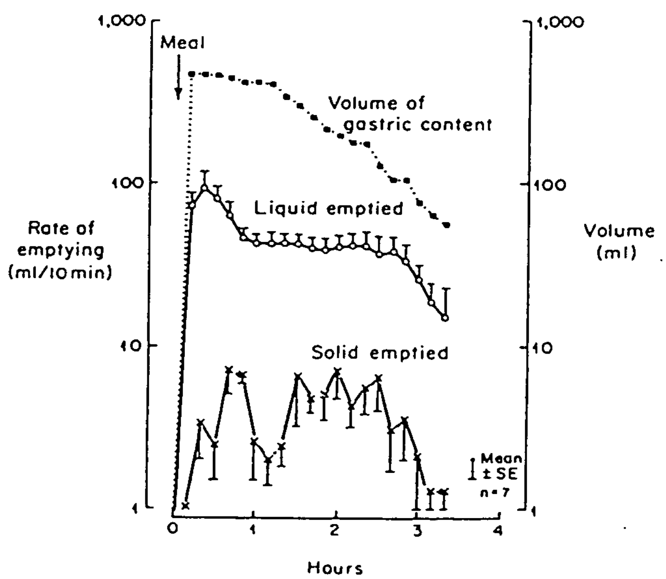
Fig. 13



Simultaneous quantification of postprandial volume of gastric contents (*a*), and its fraction being emptied into duodenum (*b*), which represents the actual gastric emptying rate.

Malagelada et al 1976

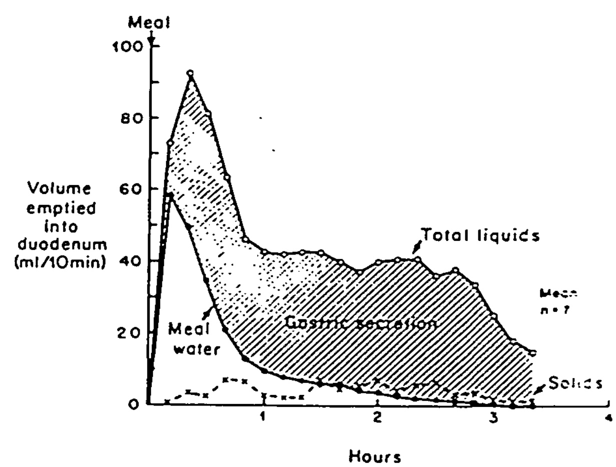
Fig. 14



Comparison between postprandial rates of gastric emptying of solids and liquids, in relation to the total volume of gastric contents. Note logarithmic scale on *vertical axis*.

Malagelada 1977

Fig. 15



Postprandial gastric emptying of various meal components.

Fig. 16

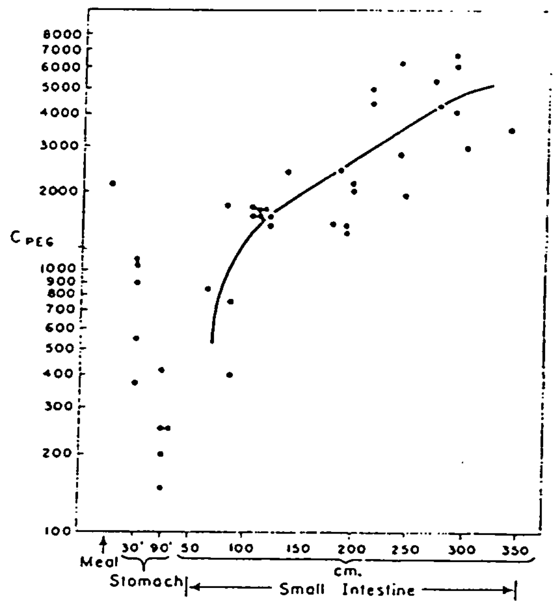


Fig. 1. Concentration (in mg. %) of polyethylene glycol (C_{PEG}) in steak-meal supernate, stomach contents (sampled at 30 and 90 min. after eating), and in intestinal fluid sampled at various distances from teeth. With intubation technic used, pylorus is at 60 cm., ligament of Treitz at 90 cm., and ileocecal valve at approximately 350 cm. from teeth. Only 2 highest values of C_{PEG} obtained following each meal have been plotted.

Fordtrans & Locklear 1966

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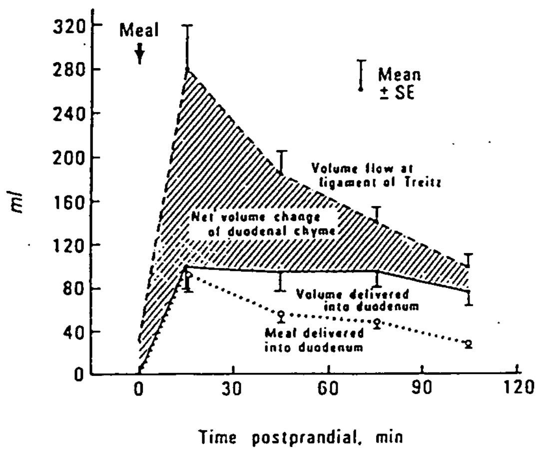
Fig. 17



Simultaneously measured postprandial volume being delivered into duodenum (——) and volume leaving duodenum at ligament of Treitz (– – –), with shaded area between these curves representing net volume change of duodenal chyme. Also plotted (· · · ·) is portion of volume delivered into duodenum which represents meal volume rather than gastric secretions.

Miller et al 1978

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AGENT : Eric Potter Clarkson.